

THE AMERICAN HEART JOURNAL



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A JOURNAL FOR THE STUDY OF THE CIRCULATION
PUBLISHED MONTHLY
UNDER THE EDITORIAL DIRECTION OF
THE AMERICAN HEART ASSOCIATION

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VOLUME 18
JULY—DECEMBER, 1939

ST. LOUIS
THE C. V. MOSBY COMPANY
1939

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Printed in the United States of America

*Press of
The C. V. Mosby Company
St. Louis*

The American Heart Journal

VOL. 18

JULY, 1939

No. 1

Original Communications

THE RELATION BETWEEN PROLONGED P-R INTERVAL AND AURICULAR FIBRILLATION IN PATIENTS WITH RHEUMATIC HEART DISEASE

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PROLONGATION of the P-R interval in rheumatic fever has been shown by Bruenn¹ to be due, in most instances, to vagal activity, which depresses A-V conduction. Since it has been known for many years that vagal stimulation also predisposes to the development of auricular fibrillation,^{2, 3, 4, 5} it was of interest to learn whether or not the incidence of that arrhythmia was unusually high in patients with rheumatic heart disease in whom evidence of increased vagal activity, as manifested by prolongation of the P-R interval, had been detected.

OBSERVATIONS

There were available for study the records of fifty-five patients with prolonged P-R intervals in whom a diagnosis of rheumatic heart disease had been established and in whom repeated electrocardiograms had been made. Twenty-one of these developed auricular fibrillation. For purposes of comparison the records of all patients with rheumatic heart disease and auricular fibrillation were also studied. These numbered 151, including the twenty-one who had a prolonged P-R interval.

In ten of the fifty-five patients with prolongation of the P-R interval to more than 0.21 seconds, the impaired A-V conduction occurred for a period of one to four days during a single attack of rheumatic fever, and was never again detected during the period of subsequent study, which varied from one month to three years. None of these patients developed auricular fibrillation.

Of the other forty-five patients of this group, a prolonged P-R interval was detected in all, or almost all, of the electrocardiograms, over a period ranging from one month to eight years. Twenty-one of these patients, or 47 per cent of the patients with a persistently prolonged

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Received for publication Nov. 25, 1938.

P-R interval, showed auricular fibrillation at one time or another. The remaining twenty-four, studied over periods ranging from one month to five years, at no time exhibited electrocardiographic evidence of auricular fibrillation, although, in two instances, paroxysms of arrhythmia, diagnosed clinically as auricular fibrillation, occurred from time to time; these two patients were not included in the fibrillation group, since electrocardiographic evidence of the arrhythmia was lacking.

Of the twenty-one patients who showed both auricular fibrillation and normal rhythm with prolonged P-R interval during their course, the fibrillation was paroxysmal, i.e., it lasted for a few hours to a few days, in five, and was chronic in sixteen. Of the sixteen cases of chronic auricular fibrillation, reversion to normal rhythm was effected in four cases, and a prolonged P-R interval then became evident. Fibrillation later recurred in these patients. In the remaining twelve cases of persistent auricular fibrillation, the onset of chronic auricular fibrillation was preceded by periods, ranging from one month to eight years, during which a prolonged P-R interval was found constantly, or almost so. Six of these patients were studied quite extensively; in all cases in this latter group, fibrillation occurred for periods of several weeks or months at a time, alternating with periods of normal rhythm, reversion taking place spontaneously. No relation was found in these cases between the onset and disappearance of auricular fibrillation or prolongation of the P-R interval, on the one hand, and symptoms of rheumatic infection, changes in degree of congestive failure, or medication, on the other. All six patients, when last seen, exhibited auricular fibrillation; there is no indication whether or not this arrhythmia is now permanently established. The following two patients (Table I), chosen because they were most carefully studied, illustrate the spontaneous variations in rhythm.

A definite increase in the percentage incidence of fibrillation was found in patients who showed prolongation of the P-R interval when the length of the period of observation following first appearance of the partial A-V block was increased.

An interesting phenomenon was observed in four of the patients with prolonged A-V conduction preceding the development of chronic auricular fibrillation; in these cases the onset of auricular fibrillation was associated with a high degree of auriculoventricular block, as manifested by idioventricular rhythm with a ventricular rate of approximately 50 beats per minute. Subsequently, the ventricular beating became quite irregular in all, although the rate remained slow.

Study of the 151 patients with rheumatic heart disease and auricular fibrillation revealed the fact that in 124 instances fibrillation was established when the patient was first seen, and remained so. Of twenty-seven patients in whom fibrillation developed under observation, twenty-one had previously shown prolongation of the P-R interval for periods ranging from one month to eight years.

The six patients in whom the onset of auricular fibrillation was not preceded by prolongation of the P-R interval are as follows:

1. Two cases in each of which a single electrocardiogram, showing normal rhythm, was obtained, respectively three and seven and one-half years before the onset of auricular fibrillation. These cases must be considered as inadequately studied.

TABLE I

CASES	DATE	ELECTROCARDIOGRAM (SECONDS)
<i>Case 1</i>	12/ 6/32	Normal Rhythm, P-R, .24
	12/30/32	Normal Rhythm, P-R, .18
	4/12/33	Normal Rhythm, P-R, .20
	4/ 3/34	Normal Rhythm, P-R, .22
	10/11/34	Normal Rhythm, P-R, .24
	1/15/35	Normal Rhythm, P-R, .24
	4/ 8/35	Normal Rhythm, P-R, .30
	6/19/35	Normal Rhythm, P-R, .24
	10/ 9/35	Normal Rhythm, P-R, .22
	1/ 3/36	Normal Rhythm, P-R, .24
	1/ 4/36	Normal Rhythm, P-R, .26
	1/ 8/36	Normal Rhythm, P-R, .24
	1/17/36	Normal Rhythm, P-R, .24
	6/29/36	Normal Rhythm, P-R, .24
	10/ 7/36	Normal Rhythm, P-R, .26
	6/ 1/37	Auricular Fibrillation
	6/ 2/37	Auricular Fibrillation
	6/ 8/37	Auricular Fibrillation
	6/21/37	Normal Rhythm, P-R, .26
	6/30/37	Normal Rhythm, P-R, .28
	7/13/37	Auricular Fibrillation
	7/14/37	Auricular Fibrillation
<i>Case 2</i>	4/12/33	Normal Rhythm, P-R, .22
	4/24/33	Normal Rhythm, P-R, .20
	5/ 4/33	Normal Rhythm, P-R, .24
	5/17/33	Normal Rhythm, P-R, .26
	5/24/33	Normal Rhythm, P-R, .24
	7/14/33	Normal Rhythm, P-R, .24
	8/14/33	Auricular Fibrillation
	8/17/33	Auricular Fibrillation
	8/19/33	Auricular Fibrillation
	9/25/33	Normal Rhythm, P-R, .28-.42
	12/19/33	Normal Rhythm, P-R, .24
	1/19/34	Normal Rhythm, P-R, .26
	4/24/34	Normal Rhythm, P-R, .22
	10/16/34	Normal Rhythm, P-R, .24
	2/16/35	Normal Rhythm, P-R, .24
	4/ 6/35	Normal Rhythm, P-R, .26
	11/ 9/35	Normal Rhythm, P-R, .26
	4/28/36	Normal Rhythm, P-R, .24
	9/23/36	Auricular Fibrillation
	11/14/36	Auricular Fibrillation
	4/24/37	Auricular Fibrillation
	12/ 4/37	Auricular Fibrillation

2. One case in which a very short P-R interval due to A-V nodal rhythm was found before the onset of fibrillation. Following the spontaneous disappearance of fibrillation, normal rhythm was associated with a prolonged P-R interval which persisted during the entire period of subsequent observation, lasting a month.

3. One case in which auricular fibrillation appeared three days after pulmonary infarction.

4. Two patients in whom a normal P-R interval was found constantly within a year preceding the onset of fibrillation. One of these was under the influence of quinidine at the time. In the other the fibrillation was paroxysmal and was apparently precipitated by the ingestion of alcohol.

DISCUSSION

In evaluating the significance of the frequent occurrence of auricular fibrillation in patients with rheumatic heart disease and evidence of increased vagal activity in the form of prolongation of the P-R interval, it is necessary to compare the incidence of fibrillation in the group studied here with that in groups of unselected cases of rheumatic heart disease. Grant,⁶ in his follow-up studies of 1,000 patients, over a ten-year period, found that auricular fibrillation developed in 8 per cent. Calculation from the data of DeGraff and Lingg,⁷ obtained in a ten-year study of patients with rheumatic heart disease, reveals its appearance in 9 per cent of patients who did not have it when first observed. The incidence of its appearance in the group of patients with prolongation of the P-R interval, who are the subject of this report, was four times as great. The difference between the incidence in the group with prolongation of the P-R interval here reported, and that of the unselected groups, is probably even greater, as some of the patients in the unselected groups who developed auricular fibrillation must have had a prolonged P-R interval. It must be concluded from the data here presented that patients with rheumatic heart disease who exhibit persistent prolongation of the P-R interval are prone to develop auricular fibrillation. Other authors, whose reports describe the development of auricular fibrillation either spontaneously or following the administration of digitalis in patients with partial A-V block, include Mackenzie,⁸ Reid,⁹ Schwartz,¹⁰ Cookson,¹¹ Orgain, Wolff, and White,¹² and Tung.¹³

About half the patients with prolongation of the P-R interval in the present series did not develop auricular fibrillation during the periods of observation, which, in some instances, were as long as five or six years. Therefore, increased vagal activity, as manifested by delayed A-V conduction, is not an invariable precursor of auricular fibrillation. This is in accord with known physiologic facts, for it has been shown^{5, 14, 15} that stimulation of the vagus nerve alone does not result in auricular fibrillation. Mines,¹⁶ in his original work on circus movement in the heart, defined the two conditions necessary for the development of auricular fibrillation, i.e., prolonged conduction time and shortened refractory period of the auricular musculature. Lewis and his co-workers^{17, 18, 19} and Andrus and Carter⁴ have shown that stimulating the vagus shortens the refractory period of auricular muscle; it does not, however, slow the rate of conduction of impulses in the auricular myo-

cardium. Vagal action is an important factor, but by itself cannot therefore be expected to cause auricular fibrillation.

Nahum and Hoff⁵ have advanced a hypothesis which attributes the development of auricular fibrillation in man to the simultaneous action of two factors, i.e., vagal activity and an E factor which acts in a manner as yet unknown. If certain other factors are already present, stimulation of the vagus nerve,^{3, 4} or the use of drugs which act through the vagus, such as acetyl-B-methylcholine⁵ or digitalis,^{8, 9, 10, 13, 20-27} may cause auricular fibrillation. Nahum and Hoff suggested that in rheumatic heart disease the E factor may be the stretching of the auricular wall or the pathologic changes in the auricular myocardium itself.^{28, 29} The relatively high incidence of auricular fibrillation in patients with prolonged P-R intervals who have been followed for a long time is to be ascribed to the fact that longer periods of observation increase the chances for the two factors responsible for the development of auricular fibrillation to occur simultaneously.

It might be argued that the increase in incidence of auricular fibrillation with longer periods of observation is not related directly to the presence of a prolonged P-R interval but may be due to the fact that both fibrillation and slowed A-V conduction time are independent expressions of the severer degrees of heart disease. Against this concept is the fact that auricular fibrillation in such patients may come and go, while the degree of damage to the heart remains constant.

Another indication of the significance of vagal activity in patients with a long P-R interval in whom auricular fibrillation develops is the finding, in four such patients in the present study, of idioventricular rhythm at the onset of the fibrillation, implying a high degree of A-V block. Of particular interest is the appearance of auricular fibrillation in one patient, here reported, following pulmonary infarction. Pulmonary embolism has been shown to cause stimulation of the vagus nerve.³⁰ Of interest, likewise, is the sequence of events in one patient in whom paroxysmal fibrillation was preceded by nodal rhythm and followed by prolongation of the P-R interval; nodal rhythm has been produced by vagal stimulation.³¹

The source of the vagal impulses which give rise to the changes in P-R interval and probably also to auricular fibrillation in rheumatic heart disease is not known. Bruenn¹ suggested that these impulses arise in the medulla; there are available at present no data concerning this possibility. It has, however, been shown that vagal impulses which affect the heart reflexly may arise from the root of the aorta,³² the auricles or great veins,³³ and the lungs.^{34, 35} That these structures are involved in rheumatic inflammatory processes is well known. Congestive failure, by raising the auricular or venous pressure and by causing pulmonary congestion, may also be a factor.

SUMMARY AND CONCLUSIONS

1. Fifty-five patients with prolonged P-R intervals associated with rheumatic heart disease were studied. Ten exhibited prolongation of the P-R interval for periods of a few days during the course of acute rheumatic fever. In forty-five cases prolongation of the P-R interval was persistent over a period ranging from one month to eight years. Approximately half the patients with persistent prolongation of the P-R interval due to rheumatic heart disease developed auricular fibrillation. More than three quarters of all patients with rheumatic heart disease who developed auricular fibrillation under observation previously showed a persistent prolongation of the P-R interval.

2. It has been shown by others that prolongation of the P-R interval in rheumatic heart disease is due to vagal activity; it appears that vagal activity is also a factor in the causation of auricular fibrillation in rheumatic cardiac patients.

3. Half of the rheumatic cardiac patients with persistent prolongation of the P-R interval do not develop auricular fibrillation. Therefore, vagal activity, by itself, is not an invariable precursor of auricular fibrillation. These facts are in accord with the hypothesis that the onset of auricular fibrillation is precipitated by the simultaneous action of two factors, i.e., vagal activity and the E factor of Nahum and Hoff.⁵

4. Rheumatic cardiac patients with a persistently prolonged P-R interval are much more likely to develop auricular fibrillation than those whose P-R interval is normal.

REFERENCES

1. Bruenn, H. G.: The Mechanism of Impaired Auriculo-Ventricular Conduction in Acute Rheumatic Fever, *AM. HEART J.* 13: 413, 1937.
2. Cushny, A. R.: Irregularity of the Heart and Auricular Fibrillation, *Am. J. M. Sc.* 141: 826, 1911.
3. Robinson, G. C.: The Influence of the Vagus Nerves on the Faradized Auricles in the Dog's Heart, *J. Exper. Med.* 17: 429, 1913.
4. Andrus, E. C., and Carter, E. P.: The Refractory Period of the Normally-Beating Dog's Auricle; With a Note on the Occurrence of Auricular Fibrillation Following a Single Stimulus, *J. Exper. Med.* 51: 357, 1930.
5. Nahum, L. H., and Hoff, H. E.: Auricular Fibrillation in Hyperthyroid Patients Produced by Acetyl-B-Methylcholine Chloride, With Observations on the Rôle of the Vagus and Some Exciting Agents in the Genesis of Auricular Fibrillation, *J. A. M. A.* 105: 254, 1935.
6. Grant, R. T.: After Histories for Ten Years of a Thousand Men Suffering From Heart Disease. A Study in Prognosis, *Heart* 16: 275, 1933.
7. DeGraff, A. C., and Lingg, C.: The Course of Rheumatic Heart Disease in Adults. III. The Influence of Auricular Fibrillation on the Course of Rheumatic Heart Disease, *AM. HEART J.* 10: 630, 1935.
8. Mackenzie, J.: The Schorstein Lectures on Auricular Fibrillation, *Brit. M. J.* 2: 869, 1911.
9. Reid, W. D.: Some Toxic Effects of Digitalis, *J. A. M. A.* 81: 435, 1923.
10. Schwartz, S. P.: Digitalis Studies in Children With Heart Disease. III. Auricular Fibrillation in Children With an Early Toxic Digitalis Manifestation, *Am. J. Dis. Child.* 39: 549, 1930.
11. Cookson, H.: The Aetiology and Prognosis of Auricular Fibrillation, *Quart. J. Med.* 23: 309, 1930.

12. Orgain, E. S., Wolff, L., and White, P. D.: Uncomplicated Auricular Fibrillation and Auricular Flutter. Frequent Occurrence and Good Prognosis in Patients Without Other Evidence of Cardiac Disease, *Arch. Int. Med.* 57: 493, 1936.
13. Tung, C. L.: Transient Auricular Fibrillation as a Toxic Manifestation of Digitalis, *AM. HEART J.* 12: 272, 1936.
14. Starr, I., Jr., Elsom, K. A., Reisinger, J. A., and Richards, A. N.: Acetyl-B-Methyleholin. I. The Action on Normal Persons With a Note on the Action of the Ethyl Ether of B-Methyleholin, *Am. J. M. Sc.* 186: 313, 1933.
15. Dameshek, W., Loman, J., and Myerson, A.: Human Autonomic Pharmacology. VII. The Effect on the Normal Cardiovascular System of Acetyl-Beta-Methylcholine Chloride, Atropine, Prostigmin, Benzedrine—With Especial Reference to the Electrocardiogram, *Am. J. M. Sc.* 195: 88, 1938.
16. Mines, G. R.: On Dynamic Equilibrium in the Heart, *J. Physiol.* 46: 349, 1913.
17. Lewis, T.: The Law of Cardiac Muscle With Special Reference to Conduction in the Mammalian Heart, *Quart. J. Med.* 14: 339, 1921.
18. Lewis, T., Drury, A. N., and Bulger, H. A.: Observations Upon Flutter and Fibrillation. VI. The Refractory Period and Rate of Propagation in the Auricle: Their Relation to Block in the Auricular Walls and to Flutter, *Heart* 8: 83, 1921.
19. Lewis, T., and Master, A. M.: Observations Upon Conduction in the Mammalian Heart. A-V Conduction, *Heart* 12: 209, 1925.
20. Cushny, A. R.: The Therapeutics of Digitalis and Its Allies, *Am. J. M. Sc.* 141: 469, 1911.
21. Mackenzie, J.: Digitalis, *Heart* 2: 273, 1911.
22. Nadel, V.: Ein Fall von Flimmerarrhythmie im Kindersalter. *Mitt. d. Gesellsch. f. inn. Med. u. Kinderh. in Wien.* 12: 210, 1913.
23. Danielopolu, D.: Arythmie complète chez l'homme, provoquée par la digitale; rôle du système modérateur, *Compt. rend. Soc. de biol.* 79: 97, 1916.
24. Resnik, W. H.: Transient Auricular Fibrillation Following Digitalis Therapy, With Observations Upon the Reaction to Atropine, *J. Clin. Investigation* 1: 181, 1924.
25. Schwartz, S. P.: The Action of Digitalis in Complete Heart Block. Its Toxic Influence on the Idioventricular Rate and Rhythm, *AM. HEART J.* 4: 408, 1929.
26. McEachern, D., and Baker, B. M., Jr.: Auricular Fibrillation. Its Etiology, Age Incidence and Production by Digitalis Therapy, *Am. J. M. Sc.* 183: 35, 1932.
27. Jezer, A., and Schwartz, S. P.: Auricular Fibrillation as an Early Toxic Digitalis Manifestation; Further Observations on This Drug in Children With Congestive Heart Failure, *J. Pediat.* 5: 811, 1934.
28. De la Chapelle, C. E., Graef, L., and Rottino, A.: Studies in Rheumatic Heart Disease. An Analysis of 119 Hearts With Special Reference to the Relationship of Auricular Fibrillation to Mitral Valvular Deformity and Certain Rheumatic Tissue Changes, *AM. HEART J.* 10: 62, 1934.
29. Gross, L.: Lesions of the Left Auricle in Rheumatic Fever, *Am. J. Path.* 11: 711, 1935.
30. Binger, C. A. L., Brow, G. R., and Branch, A.: Experimental Studies on Rapid Breathing. I. Tachypnea, Independent of Anoxemia, Resulting From Multiple Emboli in the Pulmonary Arterioles and Capillaries, *J. Clin. Investigation* 1: 127, 1924.
31. Meek, W. J., and Eyster, J. A. E.: Experiments on the Origin and Propagation of the Impulse in the Heart, *Heart* 5: 227, 1914.
32. Eyster, J. A. E., and Hooker, D. R.: Direct and Reflex Response of the Cardio-Inhibitory Centre to Increased Blood Pressure, *Am. J. Physiol.* 21: 373, 1908.
33. Bainbridge, F. A.: The Influence of Venous Filling Upon the Rate of the Heart, *J. Physiol.* 50: 65, 1915.
34. Churchill, E. D., and Cope, O.: The Rapid Shallow Breathing Resulting From Pulmonary Congestion and Edema, *J. Exper. Med.* 49: 531, 1929.
35. Schwiegk, H.: Der Lungenentlastungsreflex, *Pflüger's Arch. f. d. ges. Physiol.* 236: 206, 1935.

ROENTGENKYMOGRAPHIC STUDIES OF MYOCARDIAL INFARCTION*

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SINCE the classical description by Herrick, in 1912,¹ coronary thrombosis has become a well-recognized clinical entity. Frequently, however, the history is atypical and physical findings are minimal, while on occasion the cardinal symptom of pain may be entirely absent. In such cases additional diagnostic methods are necessary.

The electrocardiogram has proved to be an invaluable aid in the diagnosis of coronary thrombosis and is frequently the only means available for its recognition. The first description of electrocardiographic changes due to interference with coronary blood supply was given by Smith,² who ligated branches of the coronary arteries in dogs. Following these observations and those of Herrick³ and of Pardee⁴ on coronary thrombosis in man, the investigations of Parkinson and Bedford⁵ and of Barnes and Whitten⁶ established the value of the electrocardiogram in the diagnosis of coronary thrombosis, and indicated further that the site of the infarct could be localized by the electrocardiographic pattern. This work was soon corroborated by Bell and Pardee⁷ and by Levine,⁸ and was confirmed experimentally by Barnes and Mann,⁹ Crawford, Roberts, Abramson, and Cardwell,¹⁰ and by Haney, Borman, and Meek.¹¹

More recently, the electrocardiographic diagnosis and localization of myocardial infarction have been made still more precise by the employment of the precordial lead, as suggested by Wolferth and Wood,¹² and it is now well recognized that in many cases infarcts are demonstrable electrocardiographically only in the precordial lead.

In addition to the problem of diagnosis in acute coronary thrombosis, the appraisal of the extent of myocardial damage in patients who present a history suggestive of a previous coronary thrombosis, or of angina pectoris, is important. Physical findings are very often meager, and while the electrocardiogram may indicate myocardial disease, it does not show the amount of involvement; in fact, one may obtain a normal electrocardiogram when extensive damage is present. In a series of eighty-six cases of coronary artery disease studied post mortem by Willius and Brown,¹³ thirty-four of the patients, or 40 per cent, presented no clinical evidence of cardiac disease. Any additional methods which throw further light on the diagnosis of myocardial disease are, therefore, to be welcomed.

*Presented before the American Society for Clinical Investigation, May, 1938.

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Received for publication Dec. 3, 1938.

Ordinary roentgenologic examination is of little value in coronary artery disease, except to indicate cardiac enlargement and occasionally to demonstrate an aneurysm of the left ventricle secondary to myocardial infarction. The results of fluoroscopic examination, although sometimes suggestive, are far from definite.

Roentgenkymography, in contrast to plain roentgenologic examination, is a method for investigating function, rather than structure, by recording the movements of the heart throughout the cardiac cycle. In the hope that this technique might contribute more to the recognition of myocardial damage than the usual roentgenologic examination, forty-five patients with coronary thrombosis were studied with the kymograph. An attempt was made to localize and determine the extent of the infarct by changes in the contractility of the different parts of the heart as revealed in the movement phenomena.

METHOD AND INTERPRETATION

The technique employed is the same as has been described in detail by Stumpff¹⁵ and Hirsch.¹⁶ Briefly, the roentgenkymogram is obtained by interposing between the subject and the film a cassette containing a lead grid with multiple, thin, horizontal slits about 0.4 mm. wide. The only parts of the heart shadow recorded on the film, therefore, are those thin segments opposite the slits, all other rays being blocked by the impervious lead grid. If the film is moved downward during a continuous exposure, the inthrasts and outthrasts of the points of the cardiac contour exposed will be recorded on the moving film in the form of a wave, the waves being repeated with each cardiac cycle. The slits are spaced 12 mm. apart, and the film is moved just short of the distance between two slits to prevent overlapping of the waves. The movement of points of the cardiac shadow at 12 mm. intervals is thereby obtained. With an exposure of one second, one to two complete cardiac cycles are generally recorded, depending on the heart rate. When the heart rate is slow, an exposure of one and one-half to two seconds is preferable. Since the film moves down during the exposure, the time ordinate is upward. Fig. 1 illustrates the kymogram of a normal subject.

With this method, therefore, one can visualize the movement of points all along the left ventricular contour at 12 mm. intervals. Exposures taken in the posteroanterior and in the slight and full left oblique positions (about 25° and 60 to 70°, Figs. 2A, B, C) enable one to obtain a record of the contraction of the anterolateral wall, of a large part of the posterior wall of the left ventricle, and of the right ventricle in addition.

The waves of each chamber are characteristic, and are readily susceptible of physiologic interpretation.¹⁷ The aortic and pulmonary arterial waves are identical with carotid sphygmograms. The right auricular waves are multiple, and correspond to the a, c, and v waves of

the jugular pulse. The ventricular waves resemble ventricular volume curves. Johnson¹⁸ has found a close correspondence between the amplitude of the ventricular wave and the stroke volume, as determined by the dye method. However, the ventricular wave is not a true volume

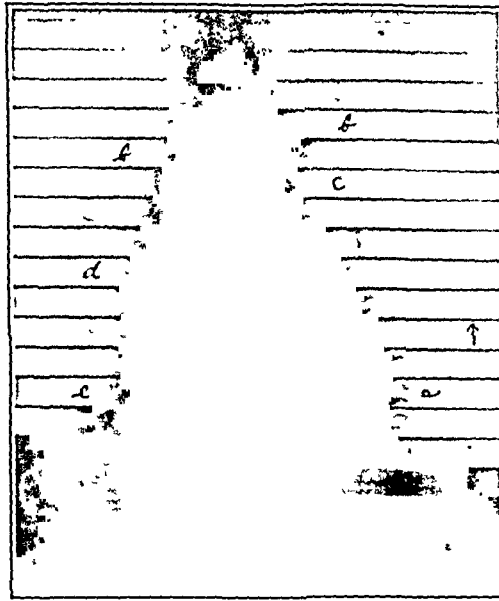
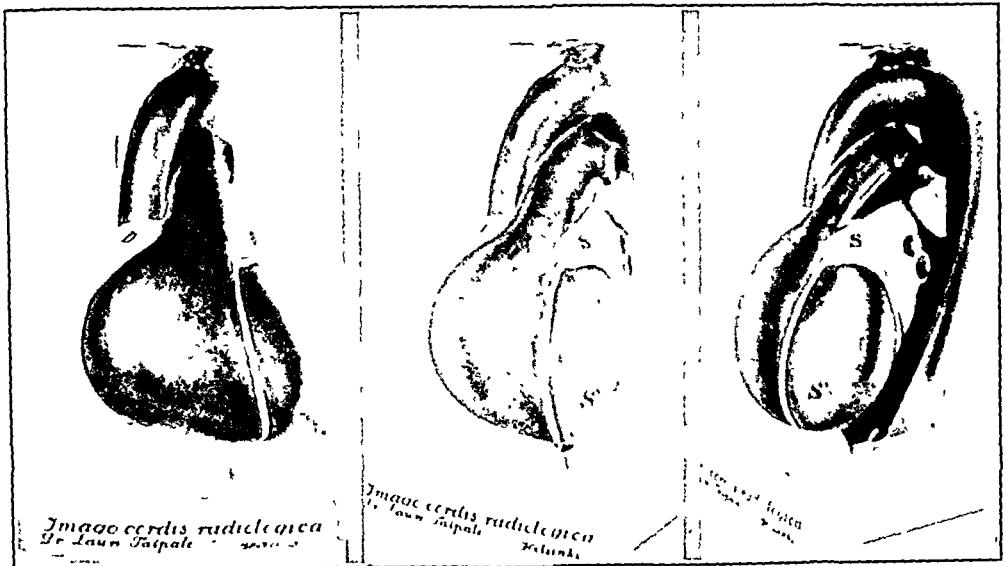


Fig. 1.—Normal kymogram.



A.

B.

C.

Fig. 2.—Anatomic relationships of the various chambers in the different views in which kymograms were taken, illustrating particularly the area of the left ventricle visualized. A, Posteroanterior; B, slight left oblique; C, full left oblique.

record for the following reasons: (1) The kymogram is taken at a distance of 3 feet, and there is therefore some magnification. (2) Due to the oblique position of the heart border on the left side, its movements, recorded through a horizontal slit, are distorted. This may, however, be easily corrected for and the true amplitude obtained (Fig. 3). (3)

In addition to the predominant contractile movement of the ventricle, there are other movements as well, i.e., elevation of the apex and positional changes of the heart as a whole.

The movement of the apex is particularly variable, and is reduced in cardiac decompensation because of the impaired contraction of the ventricle as a whole, with a consequent diminution or loss of the normal upward apical thrust. Furthermore, as Kirch¹⁹ has emphasized, the apex is the most labile portion of the ventricle, and atrophy and thinning of the apex with loss of contractility occur in cardiac enlargement with heart failure of whatever cause. Esser²⁰ has clearly shown that reverse pulsations may occur at the apex when the heart is greatly dilated. For this reason great caution must be observed in interpreting diminution or absence of pulsations in this region as indicative of infarction. The great majority of the hearts included in this series, however, were not markedly enlarged, so that this criticism does not invalidate the findings. The only condition we have encountered in a heart of about normal size, other than coronary thrombosis, in which there was no visible contraction of the left ventricle, was constrictive pericarditis (diagnosis confirmed at operation).

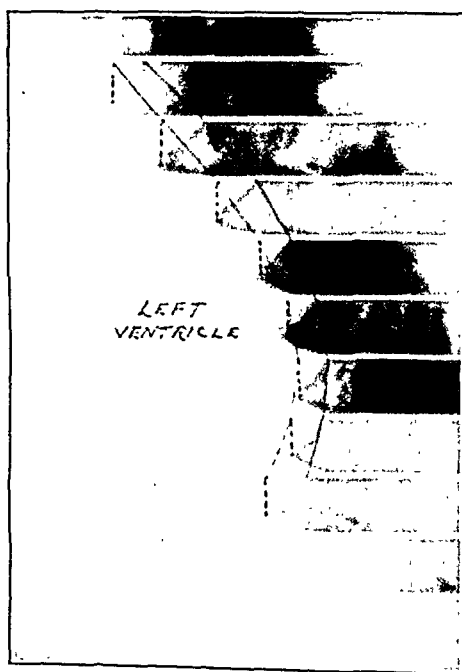


Fig. 3.—Outline of left ventricle in systole and diastole. Since the contour of the heart is not perpendicular to the slit at all points, in order to estimate the amplitude of contraction the crests and troughs of the waves must be brought to the same horizontal level.

Recognizing the limitations of the ventricular wave as an index of volume changes, the amplitude of the waves, nevertheless, reflects, with fair accuracy, the contraction of individual portions of the ventricle, and the failure of localized areas to contract becomes significant. When

there is definite reversal of the waves in a certain region, as was the case in a large percentage of the present series, the interpretation that this is the site of infarction seems valid. Similarly, when there is a sudden change from active to practically absent pulsation, one appears justified in assuming that the contractility of this region is actually markedly impaired; indeed, at times one observes active contraction both above and below the area of absent pulsation. In an extensive experience with kymography in various types of heart disease other than coronary thrombosis, we have observed a reversal of pulsation only once, in a case of rheumatic mitral disease. The heart was only moderately enlarged, and the reason for the reverse pulsation in the apical region is not clear. The most likely causes would seem to be alteration of the movement of the heart as a whole, or impaired contractility due to extensive damage in this region.

Most of the records were taken during convalescence, as soon as the patient was able to get out of bed. It has thus far not been possible to check the findings by post-mortem examination, since none of the patients has yet come to autopsy. However, the kymographic findings were compared with the electrocardiographic localization, precordial leads being taken, in addition to the standard leads, in all cases. Levine, Lowman, and Wissing¹⁴ have recently reported a series of 140 cases which were studied fluoroscopically. In some of the cases posteroanterior kymograms were made, but no oblique views were taken. The radiologic diagnosis of coronary disease was confirmed electrocardiographically in 75 per cent of the cases. No statement was made concerning localization of the infarcts. In twelve cases in which autopsy was performed the electrocardiographic diagnosis was confirmed in eleven and the roentgenologic in ten.

RESULTS

Table I summarizes the roentgenkymographic and electrocardiographic findings in forty-five cases of coronary thrombosis.

In the first two cases listed in the table there could be no doubt about the nature of the anatomic lesion. A diagnosis of ventricular aneurysm was made clinically and confirmed by ordinary roentgenologic and kymographic examinations in both of these cases.

Fig. 4, *A* to *C*, shows the roentgenogram, the roentgenkymogram, a graphic correlation of the waves on a time axis, and the electrocardiogram, in Case 1. This patient had had four attacks of coronary thrombosis, and had a distinct thrust over a wide area of the precordium. The diagnosis of ventricular aneurysm was confirmed roentgenologically (Fig. 4*A*). The kymogram (Fig. 4*C*) shows a complete reversal of contraction over the aneurysmal area, i.e., while the rest of the ventricle contracts this segment distends as a passive sac, collapsing at the end of systole when the fall of intraventricular pressure relieves the tension on the aneurysmal area. This reverse movement is clearly shown in the graphic correlation of the waves in Fig. 4*B*.

The first phase of the contraction of the heart is the contraction of the atria. This is followed by the contraction of the ventricles. The contraction of the atria is initiated by the sinoatrial node, which is located in the right atrium. The contraction of the ventricles is initiated by the atrioventricular node, which is located in the septum between the two ventricles.

The contraction of the atria is a rapid, forceful contraction. It is followed by a period of relaxation. The contraction of the ventricles is a slower, more powerful contraction. It is followed by a period of relaxation. The contraction of the ventricles is the most important phase of the cardiac cycle, as it is the only phase in which the heart actually pumps blood out to the body.

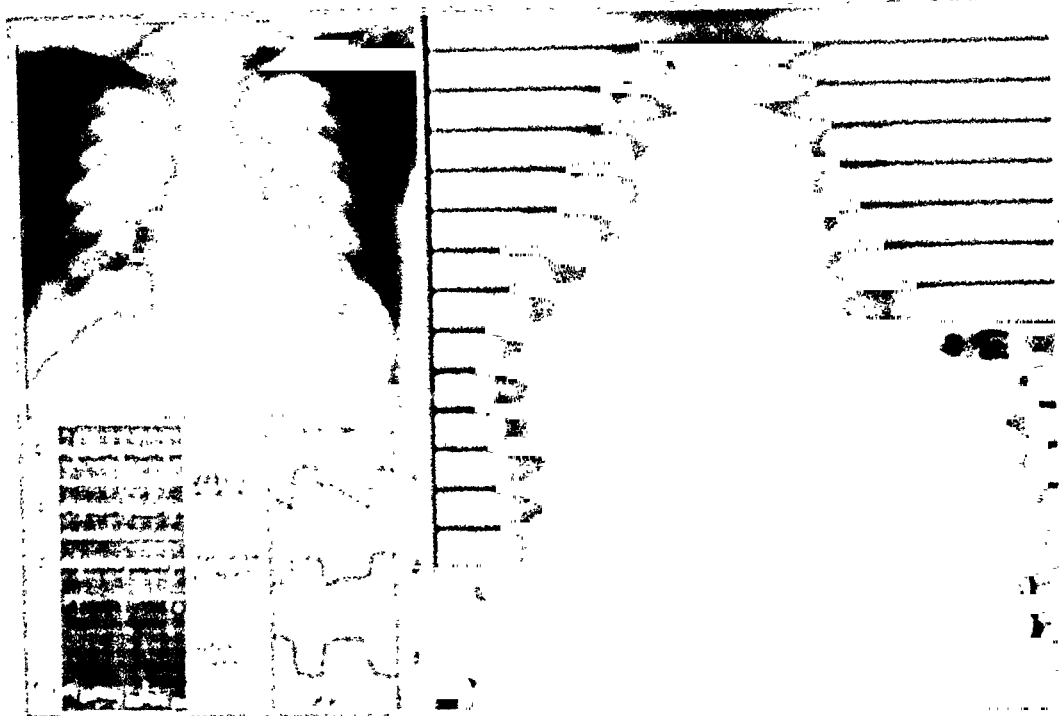


FIG. 1. Fluoroscopic view of the heart and electrocardiogram (ECG) trace. The trace shows the P, Q, R, S, T, and U waves, which correspond to the electrical activity of the heart during the cardiac cycle.

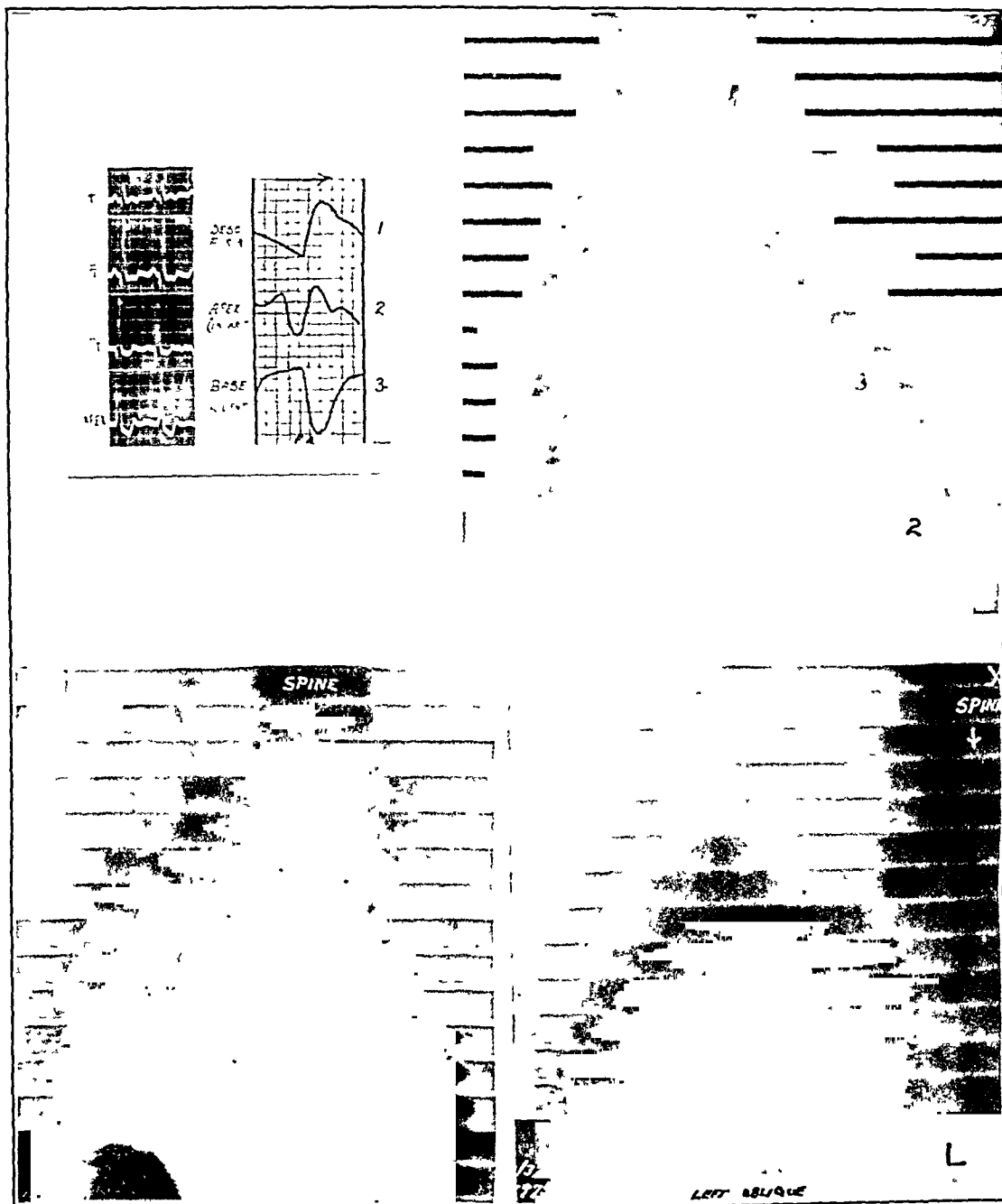
FIG. 2. A series of fluoroscopic views of the heart during the cardiac cycle. The views show the heart's position and shape at different points in time. The first view shows the heart in a relaxed state. The second view shows the heart during the contraction of the atria. The third view shows the heart during the contraction of the ventricles. The fourth view shows the heart during the relaxation phase. The views are labeled 'A', 'B', 'C', 'D', 'E', 'F', 'G', 'H', 'I', 'J', 'K', 'L', 'M', 'N', 'O', 'P', 'Q', 'R', 'S', 'T', 'U', 'V', 'W', 'X', 'Y', 'Z'.

normality in the posteroanterior view (Fig. 6C). The kymogram thus indicates an infarct of the midsection of the posterolateral wall of the left ventricle.

Group 2.—In the 6 cases of Group 2 the kymogram showed involvement of both anterior and posterior walls. The electrocardiographic

A.

B.



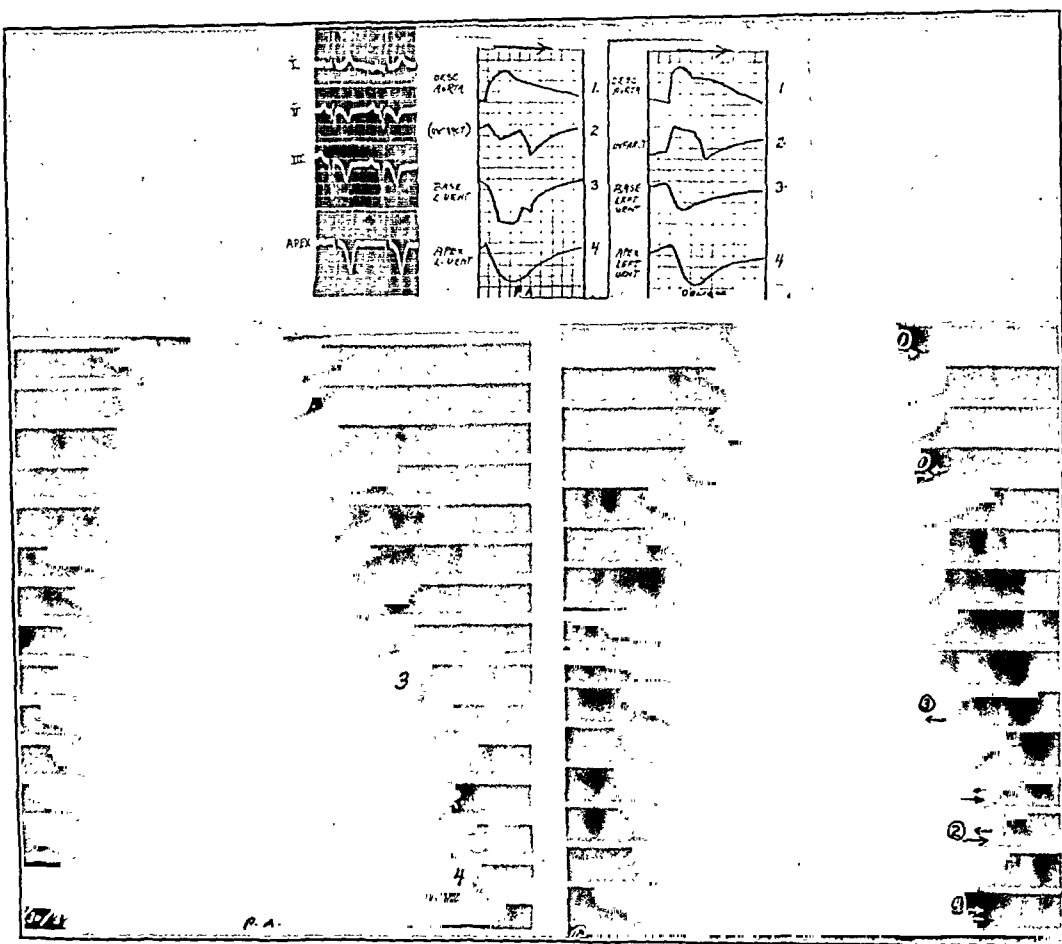
C.

D.

Fig. 5.—Anterior wall infarction. A, Electrocardiogram showing Q₁ T₁ pattern and correlation of kymographic waves on a time axis; B, posteroanterior kymogram showing reversal of waves at apex; C, slight left oblique—normal waves; D, full left oblique—normal waves.

localization was posterior wall in 4 cases and anterior wall in 2 cases. Extensive areas of infarction were revealed by the kymogram. Fig. 7, *B* and *C*, illustrates an area of infarction in the midsection anteriorly and posteriorly. The posteroanterior view shows reverse movement of four segments (Fig. 7*B*). In the slight left oblique view there is also reverse movement at the same level (Fig. 7*C*). The electrocardiographic changes in this case indicated involvement of the posterior wall (Fig. 7*A*).

A.



B.

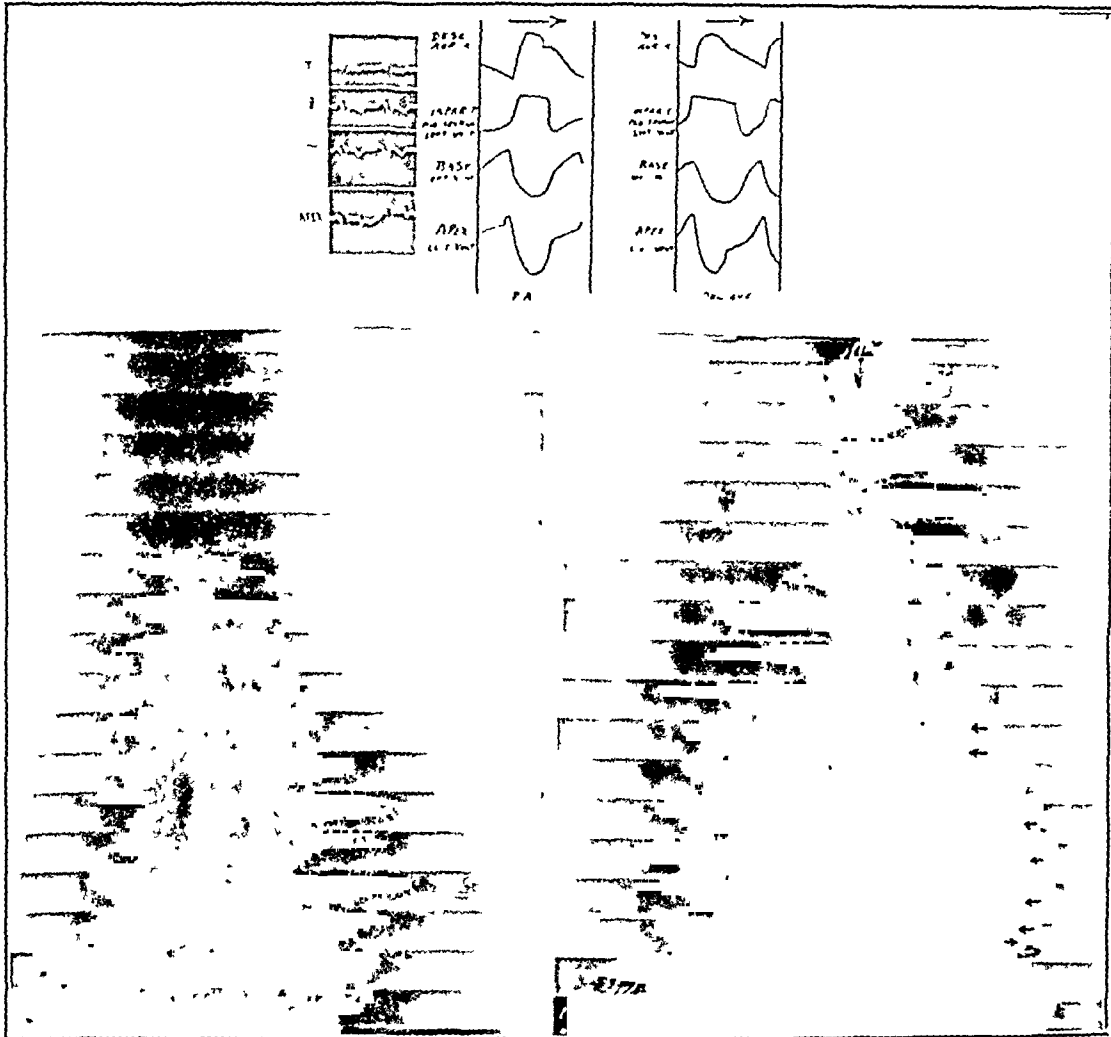
C.

Fig. 6.—Posterior wall infarction. *A*, Electrocardiogram showing Q_3 T_3 pattern and correlation of kymographic waves on a time axis; *B*, posteroanterior kymogram, impaired contractions at midsection; *C*, slight left oblique, reversal of waves in midsection.

Group 3.—Five cases in which the kymographic and electrocardiographic findings did not agree comprise this group. The electrocardiogram indicated posterior wall infarction in 4 cases and anterior wall infarction in 1 case. The kymograms showed an infarct of the anterior wall in one case in which the electrocardiogram suggested posterior wall infarction, and nothing abnormal in the other 4 cases. Possibly the

site of infarction was not registered in the kymogram because the area involved was too small or not included in the part recorded. There is a small area close to the septum, in the region of the diaphragm, which cannot be seen in the views included in this study. It is apparent that there is better correspondence with anterior than with posterior wall infarcts. This is probably due to the easier visualization of the anterior wall in the kymogram.

A.



B.

C.

Fig 7—Anterior and posterior wall infarction. A, Electrocardiogram showing changes in all leads, suggestive more of posterior wall involvement, and correlation of kymographic waves on a time axis; B, posterioranterior, reversal of waves in midsection; C, slight left oblique, reversal of waves in midsection.

Group 4.—This comprised 3 cases in which no localization was possible electrocardiographically because of bundle branch block, except that one could say that the septum was involved. The kymogram showed an area of infarction of the anterior ventricular wall in two cases, and of both anterior and posterior walls in one case.

TABLE I

CASE		AGE	NUMBER AND SEVERITY OF ATTACKS	ELECTROCARDIOGRAPHIC LOCALIZATION	KYMOGRAPHIC LOCALIZATION
1.	F. A.	55	4th attack, ventricular aneurysm	Anterior wall	Anterior wall, upper half (reverse movement)
2.	M. M.	59	1st attack ventricular aneurysm	Posterior wall	Anterior wall, and posterior wall, lower third (reverse movement in posteroanterior; absent movement in oblique)
3.	B. W.	57	1st attack, severe, heart failure	Anterior wall	Anterior wall Aneurysmal dilatation of midsection with absent to slightly reverse movement
4.	C. C.	52	2nd attack	Anterior wall	Anterior wall, lower half (absent movement)
5.	M. H.	56	4th attack	Anterior wall	Anterior wall, apex (reverse movement)
6.	A. B.	69	3rd attack, severe	Anterior wall (intermittent auricular flutter and fibrillation)	Anterior wall near apex (diminished to absent movement)
7.	G. S.	38	1st attack	Anterior wall	Anterior wall, apical region extending to posterior wall in lowermost segments (reverse movement in posteroanterior, absent movement in oblique)
8.	J. S.	44	1st attack	Anterior wall	Anterior wall, upper half (reverse movement)
9.	W. B.	58	1st attack	Anterior wall	Anterior wall, lower half extending to posterior wall in lowest segments (absent movement)
10.	J. S.	57	1st attack	Anterior wall	Anterior wall, upper third (reverse movement)
11.	S. W.	60	1st attack	Anterior wall	Anterior wall, apex (greatly diminished movement)
12.	W. M.	43	1st attack	Anterior wall	Anterior wall apex (practically absent movement)
13.	A. R.	72	2nd attack	Probable anterior wall	Anterior wall, upper half (reverse movement)
14.	M. K.	44	4th attack	Anterior wall	Anterior wall, entire (absent to slightly reverse movement)
15.	M. J.	40	2nd attack	Anterior wall	Anterior wall, lower half (reverse movement)
16.	C. W.	49	1st attack	Anterior wall	Anterior wall, apical region (greatly diminished movement)
17.	M. M.	53	1st attack	Anterior wall	Anterior wall, midsection (diminished movement)
18.	J. C.	55	1st attack	Anterior wall	Anterior wall, lower $\frac{2}{3}$ (reverse movement)
19.	L. G.	36	1st attack	Anterior wall	Anterior wall, upper half (reverse movement)

TABLE I (CONTINUED)

CASE		AGE	NUMBER AND SEVERITY OF ATTACKS	ELECTROCARDIO- GRAPHIC LOCALIZATION	KYMOGRAPHIC LOCALIZATION
20.	E. S.	76	?	Anterior wall	Anterior wall, lower $\frac{2}{3}$ (reverse movement)
21.	M. M.	42	1st attack, embolization to right leg	Probable posterior wall	Posterior wall, upper $\frac{2}{3}$ Anterior wall, upper $\frac{1}{4}$ (reverse movement)
22.	P. B.	62	1st attack	Posterior wall	Posterior wall, midsection (reverse movement)
23.	S. G.	63	1st attack	Posterior wall	Posterior wall, midsection (reverse movement)
24.	A. A.	55	1st attack	Posterior wall	Posterior wall, upper $\frac{2}{3}$ (reverse movement)
25.	A. Z.	46	1st attack	Anterior wall	Lateral wall, lower half (absent movement)
26.	N. S.	63	1st attack	Posterior wall	Posterior wall, midsection (partial reverse movement)
27.	J. S.	70	1st attack, angina 13 yr.	Posterior wall	Anterior wall, lower half Posterior wall, lowest segments (absent movement in posteroanterior, reverse movement in oblique)
28.	H. S.	50	1st attack, severe	Anterior wall	Anterior wall, lower half Posterior wall, lower third (reverse movement)
29.	C. S.	49	1st attack	Posterior wall	Anterior wall, apical region Posterior wall, lower $\frac{1}{4}$ (Reverse movement in posteroanterior, absent movement in $\frac{1}{2}$ oblique, partial reverse movement in full oblique)
30.	M. S.	52	1st attack	Posterior wall	Anterior wall, midsection Posterior wall, midsection (reverse movement)
31.	W. W.	61	1st attack	Anterior wall Intraventricular conduction disturbance	Anterior wall, midsection Posterior wall, midsection (diminished movement)
32.	G. O.	43	1st attack 3 years ago. Intermittent decompensation since	Right bundle branch block	Anterior wall, lower half (reverse movement) Posterior wall—not clear
33.	A. S.	66	1st attack	Possible septal infarct Periods of nodal rhythm and of left bundle branch block	Anterior wall, apex (greatly diminished to absent movement)
34.	L. S.	64	1st attack, severe	Left bundle branch block	Anterior wall—segment above apex Posterior wall—lower half (reverse movement)
35.	J. S.	52	1st attack	Posterior wall	Anterior wall—apical region (absent movement)

TABLE I (CONTINUED)

CASE	AGE	NUMBER AND SEVERITY OF ATTACKS	ELECTROCARDIOGRAPHIC LOCALIZATION	KYMOGRAPHIC LOCALIZATION	
36.	U. T.	40	1st attack	Posterior wall	Normal
37.	M. Y.	75	1st attack	Posterior wall	Normal
38.	M. B.	45	1st attack	Anterior wall	Normal
39.	M. D.	46	1st attack	Posterior wall	Normal
40.	L. M.	52	Angina 6 yr. Decompensation 2 yr.	Myocardial damage	Anterior wall, lower $\frac{2}{3}$ (reverse movement)
41.	H. R.	53	Severe angina 5 yr.	Myocardial damage Extensive changes	Anterior wall, lower $\frac{1}{2}$ Lateral wall, lower $\frac{2}{3}$ Posterior wall, lower $\frac{1}{2}$ (reverse movement)
42.	W. L.	73	Angina 10 yr. Impaired cardiac reserve 7 yr.	Normal, T ₁ diphasic	Anterior wall, lower $\frac{1}{2}$ Lateral wall, normal Posterior wall, mid-section (reverse movement)
43.	W. W.	40	Heart failure, hypertensive	Myocardial damage	Anterior wall, lower $\frac{1}{2}$ (reverse movement)
44.	B. T.	64	2nd attack	Myocardial damage	Anterior wall—apex Posterior wall—midsection (slightly reverse movement)
45.	W. N.	41	Hypertension aortic aneurysm	Marked myocardial changes	Anterior wall—midsection Posterior wall—midsection (partial reverse)

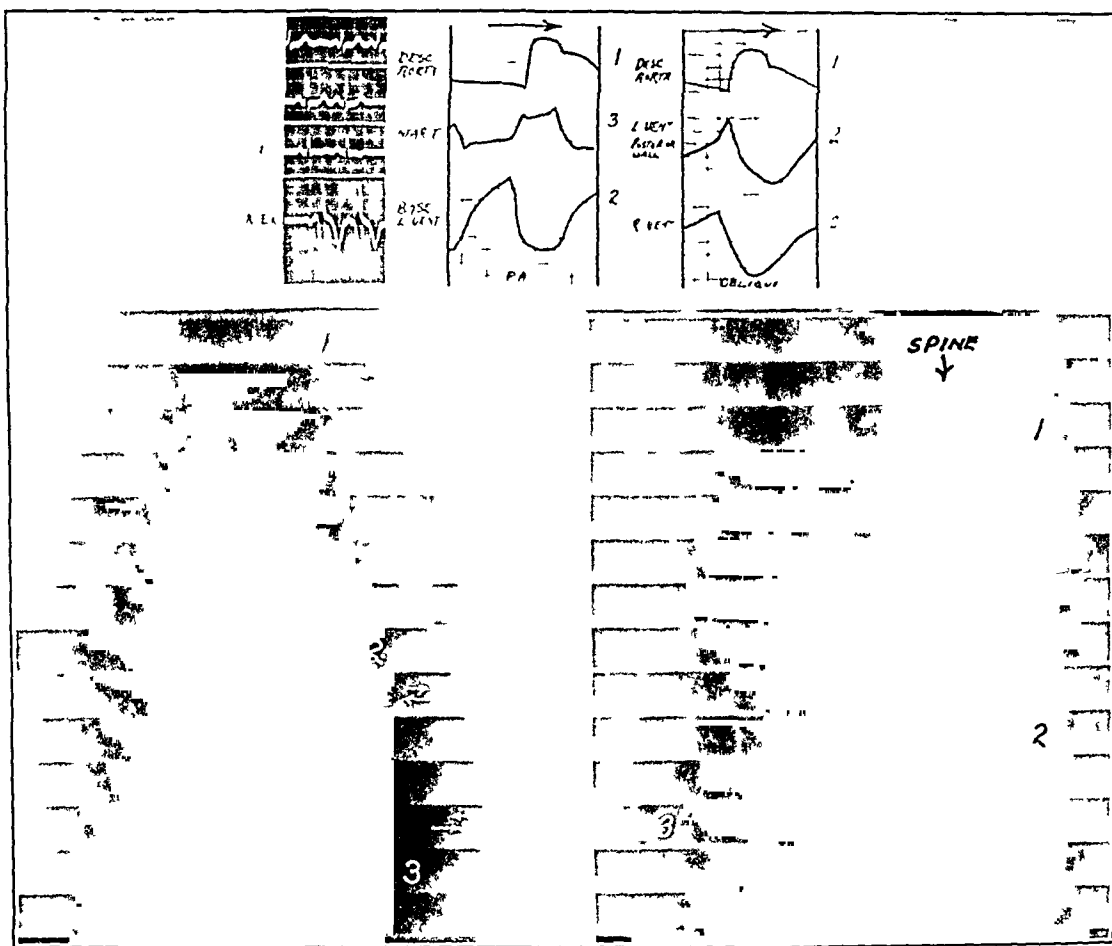
TABLE II

Group 1:		Agreement in Localization		25 Cases
	Anterior wall		20 Cases	
	Posterior wall		5 Cases	
Group 2:		Partial Agreement		6 Cases
EKG:	Posterior wall		4 Cases	
	Anterior wall		2 Cases	
Kymogram:	Anterior and posterior walls—in all		6 Cases	
Group 3:		Disagreement		5 Cases
EKG:	Posterior wall		4 Cases	
	Anterior wall		1 Case	
Kymogram:	Anterior wall		1 Case	
	Normal		4 Cases	
Group 4:		No Localization Possible From EKG		5 Cases
EKG:	Bundle branch block		3 Cases	
Kymogram:	Anterior wall		2 Cases	
	Posterior wall		1 Case	
Group 5:		Coronary Disease		6 Cases
		(No Definite Infarct Clinically or in EKG)		
EKG:	Myocardial damage		5 Cases	
	Normal		1 Case	
Kymogram:	Anterior wall		3 Cases	
	Anterior and posterior walls		3 Cases	
Total				45 Cases

Group 5.—A group which is of particular interest comprises 6 cases of coronary artery disease in which a diagnosis of myocardial infarction

could not be made clinically or from the electrocardiogram. In all of these the kymogram revealed an area of infarction; in 3, the anterior wall was involved, and in 3 both anterior and posterior walls. Fig. 8, *B* and *C*, shows the kymograms in this type of case. There is a definite reversal of movement of the lower half of the anterior wall of the left ventricle, with normal contraction over the entire ventricle in the oblique view. The patient was a man 73 years of age with a long-standing history of angina pectoris and impaired cardiac reserve. He gave no history of an attack suggesting coronary artery thrombosis. There was no

A.



B.

C.

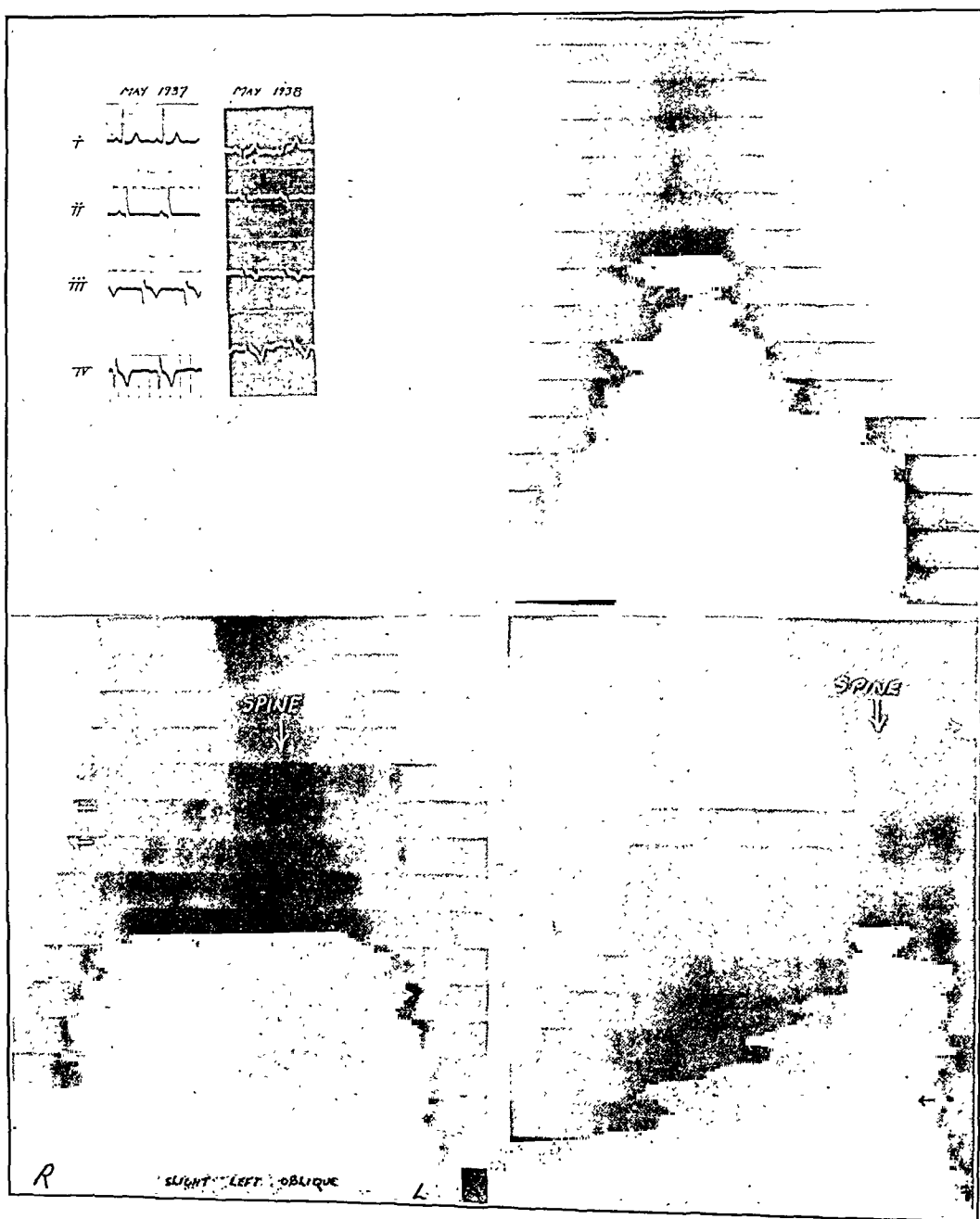
Fig 8—Anterior wall infarction in patient, age 73 years, with normal electrocardiogram. A, Normal electrocardiogram and correlation of kymographic waves on a time axis, B, posteroanterior, reversal of waves at apex, C, left oblique, normal waves.

cardiac enlargement. The electrocardiogram (Fig. 8A) gave no hint of myocardial infarction. Levine and Levine²¹ studied a group of 44 patients with angina pectoris who were subsequently autopsied, and found that "myocardial infarction is not uncommon in angina pectoris when there is no clinical evidence of a previous coronary thrombosis."

Not infrequently, some months after an acute attack of coronary thrombosis the electrocardiogram may return practically to normal. Under these circumstances an area of myocardial infarction may still be detected in the kymogram. The first of the two electrocardiograms

A.

B.



C.

D.

Fig. 9.—Posterior wall infarction in patient who showed Q_3 T_3 electrocardiographic pattern and in whom a year later the electrocardiogram reverted sufficiently toward normal to cause confusion if this had been the only record available. A, Electrocardiograms at intervals of one year; B, posteroanterior, normal waves; C, slight left oblique, reversal of waves in midsection; D, full left oblique, normal waves.

in Fig. 9A, taken during the acute attack of coronary thrombosis, was of the $Q_3 T_3$ type indicative of posterior wall infarction. The second electrocardiogram, taken one year later, shows little abnormality except for the deep Q wave in Lead III. The kymograms (Fig. 9, B to D), taken at the time of the second electrocardiogram, show normal movement of the left ventricle in the posteroanterior and in the full left oblique positions (Fig. 9, B and D). In the slight left oblique view, however, there is a distinct reversal of pulsation of some segments, indicating infarction of the lateral wall of the left ventricle (Fig. 9C).

DISCUSSION

An experimental basis for the kymographic study of myocardial infarction is afforded by the work of Tennant and Wiggers.²² These investigators studied, by means of the myocardiograph, the effect of occluding branches of the coronary arteries in the dog on the contractility of the area supplied. They found that almost immediately after occluding a particular vessel the region involved ceased to contract, and reversal of movements took place. While the rest of the ventricle contracted normally during systole, the ischemic area was distended by the raised intraventricular systolic pressure.

As seen in the cases illustrated, varying types of movement are found in areas of infarction. Most frequently, reversal, partial reversal, or absence of movement is observed. Occasionally, multiple, small, bizarre waves are present. It is difficult to explain why in one case the pulsations are absent and in another reverse pulsations occur. Both types may even occur in different segments in the same patient. A possible explanation lies in the varying degree of endocardial lamination of the infarct with mural thrombi; such lamination occurs in over one-half of all cases of coronary thrombosis, according to the observations of Applebaum and Nicolson.²³ In those cases in which the pulsations are absent there may be dense mural thrombi, whereas reverse pulsations are more likely to occur when, because there is no mural thrombus, the thinned area of infarction can distend with the systolic rise of intraventricular pressure. Indirect evidence for this was afforded in a case of aortic aneurysm in which there was no aortic pulsation in the kymogram. At post-mortem examination a densely laminated clot was found in the aneurysmal sac.

A frequent finding over normal as well as abnormal regions of the ventricle in coronary thrombosis is the disappearance of a small serration superimposed on the ventricular wave. This normally occurs at the onset of systole and is synchronous with the first heart sound.¹⁵ It probably reflects a positional change of the heart with the sudden rise of intraventricular pressure during the isometric phase of ventricular systole. Its disappearance in coronary thrombosis, as well as

in other kinds of myocardial disease, is possibly due to a less abrupt rise of intraventricular pressure.

SUMMARY

Forty-five cases of myocardial infarction were studied with the multiple-slit, moving-film kymograph. Exposures were made in the postero-anterior and two left oblique positions, thus visualizing the movements of the anterior and posterolateral walls of the left ventricle.

The technique is considered briefly and the physiologic interpretation of the ventricular wave as an index of ventricular volume changes is discussed.

The changes observed varied from reversal of movement to absence of pulsation in the infarcted area, and correspond to those recorded by Tennant and Wiggers with the myocardiograph in experimental myocardial infarction in dogs. A comparison was made between kymographic and electrocardiographic localizations in 45 cases. In 41 of the 45 cases there were definite kymographic changes. In 25 the electrocardiographic and kymographic localizations corresponded exactly. In 6 cases the kymogram indicated involvement of both anterior and posterior walls, whereas the electrocardiogram suggested infarction of one or the other. In 3 cases in which no electrocardiographic evidence of damage to the ventricular wall could be obtained because bundle branch block was present, the kymogram showed an area of infarction. In 1 case the electrocardiographic and kymographic localizations disagreed, and in 4 cases with definite coronary thrombosis the kymograms were entirely normal. In 3 of these 4 cases, the infarction was of the posterior wall. In general, localization appeared more accurate with anterior wall infarcts than with posterior wall infarcts, probably due to better visualization of the anterior wall of the left ventricle.

Six patients with coronary artery disease without definite clinical or electrocardiographic evidence of coronary thrombosis showed kymographic changes indicative of an area of infarction.

CONCLUSION

Multiple-slit roentgenkymography is a simple and valuable aid in the diagnosis of myocardial infarction. With its use one is enabled to localize and determine the extent of the infarcted area. Occasionally, as in angina pectoris, or after the subsidence of an acute attack of coronary thrombosis, it may be the only method which will demonstrate that infarction has occurred.

We wish to thank Doctor Richard A. Rendich and the members of the staff of the x-ray department of Kings County Hospital for their assistance in this work, and the physicians of Kings County Hospital for permission to study patients under their care.

REFERENCES

1. Herrick, J. B.: Clinical Features of Sudden Obstruction of the Coronary Arteries, *J. A. M. A.* 59: 2015, 1912.
2. Smith, F. M.: The Ligation of Coronary Arteries With Electrocardiographic Study, *Arch. Int. Med.* 22: 8, 1918.
3. Herrick, J. B.: Thrombosis of the Coronary Arteries, *J. A. M. A.* 72: 387, 1919.
4. Pardee, H. E. B.: An Electrocardiographic Sign of Coronary Artery Obstruction, *Arch. Int. Med.* 26: 244, 1920.
5. Parkinson, J., and Bedford, D. E.: Successive Changes in Electrocardiogram After Cardiac Infarction, *Heart* 14: 195, 1928.
6. Barnes, A. R., and Whitten, M. B.: Study of the R-T Interval in Myocardial Infarction, *AM. HEART J.* 5: 142, 1929.
7. Bell, A., and Pardee, H. E. B.: Coronary Thrombosis, Report of 2 Cases With Electrocardiographic Localization of Thrombus in Right or Left Coronary Arteries, *J. A. M. A.* 94: 1555, 1930.
8. Levine, S. A.: Coronary Thrombosis; Its Various Clinical Features, *Medicine* 8: 245, 1929.
9. Barnes, A. R., and Mann, F. C.: Electrocardiographic Changes Following Ligation of Coronary Arteries of Dog, *AM. HEART J.* 7: 477, 1932.
10. Crawford, J. H., Roberts, G. H., Abramson, D. I., and Cardwell, J. C.: Localization of Experimental Ventricular Myocardial Lesions by Electrocardiogram, *AM. HEART J.* 7: 627, 1932.
11. Hancy, H. F., Borman, B. C., and Meek, W. J.: Relation between Position of Experimental Myocardial Lesions in Dog and Changes in RS-T Segment of Electrocardiogram, *Am. J. Physiol.* 106: 64, 1933.
12. Wolferth, C. C., and Wood, F. C.: Electrocardiographic Diagnosis of Coronary Occlusion by Use of Chest Leads, *Am. J. M. Sc.* 183: 30, 1932.
13. Willius, F. A., and Brown, G. E.: Coronary Sclerosis; An Analysis of 86 Necropsies, *Am. J. M. Sc.* 168: 165, 1924.
14. Levine, G., Lowman, R. M., and Wissing, E. G.: The Roentgenologic and Electrocardiographic Diagnosis of Coronary Disease, *AM. HEART J.* 16: 133, 1938.
15. Stumpf, P., Weber, H. H., and Wertz, G. A.: Roentgenkymographische Bewegungslehre innerer Organe, Leipzig, 1936, Georg Thieme.
16. Hirsch, I. S.: Recording of Cardiac Movements and Sounds by Roentgen Ray, *Radiology* 22: 403, 1934.
17. Hirsch, I. S., and Gubner, R.: Application of Roentgenkymography to Study of Normal and Abnormal Cardiac Physiology, *AM. HEART J.* 12: 413, 1936.
18. Johnson, S. E.: Roentgen Kymography Considered in Relation to Heart Output and New Heart Index, *Am. J. Roentgenol.* 37: 167, 1937.
19. Kirch, E.: Pathogenese und Folgen der Dilatation und der Hypertrophie des Herzens, *Klin. Wchnschr.* 9: 817, 1930.
20. Esser, C.: Über das kymographische Verhalten der Herzspitze bei ausgesprochener Dilatation, *Fortschr. a. d. Geb. d. Röntgenstrahlen* 52: 213, 1935.
21. Levine, H. D., and Levine, S. A.: Electrocardiographic Study of Lead IV With Special Reference to Findings in Angina Pectoris, *Am. J. M. Sc.* 191: 98, 1936.
22. Tennant, R., and Wiggers, C. J.: Effect of Coronary Occlusion on Myocardial Contraction, *Am. J. Physiol.* 112: 351, 1935.
23. Applebaum, E., and Nicolson, G. H. B.: Occlusive Diseases of Coronary Arteries; Analysis of Pathological Anatomy in 168 Cases, With Electrocardiographic Correlation in 36 of These, *AM. HEART J.* 10: 662, 1935.

THE VALUE AND SIGNIFICANCE OF MULTIPLE CHEST LEADS IN MAN

I. NORMAL AND HYPERTROPHIED HEARTS*

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CHEST leads may be defined as leads in which one electrode is placed on some part of the chest and the other is applied in such a way that it is little affected by electrical events occurring in the heart. The various chest leads used in clinical electrocardiography^{1-8, 10, 11} have been devised to place the chest electrode near the heart. Their diagnostic significance is presumably due to the proximity of the chest electrodes to regions of the heart which have little influence on the standard limb leads.^{1, 2, 12}

Diagnostic criteria derived empirically from such leads have greatly enhanced the clinical value of electrocardiography. The use of at least one chest lead appears indispensable for the early diagnosis of cardiac infarcts,^{1, 2, 13-21} and frequently aids in detecting the presence of other forms of myocardial involvement.^{3, 17, 18, 22-29}

The clinical usefulness of multiple chest leads, however, is not yet well established in spite of several recent series of studies on this subject. Controversial opinions as to the nature of chest leads have made it difficult to evaluate their significance.^{6, 9, 10, 11, 30}

The present study represents an attempt to obtain more information concerning the electrical field surrounding the heart by exploring two horizontal cross sections of this field with chest leads, in accordance with the field theory developed by us.¹² It was hoped that with such information multiple chest leads might gain diagnostic significance beyond their purely empirical associations.

METHODS

In a total of about 200 cases of all types, multiple anterior chest leads were analyzed, and in some 50 cases both anterior and posterior chest leads were studied. This report deals only with anterior chest leads in 25 cases and both anterior and posterior chest leads in 23 cases. All 25 subjects examined with anterior chest leads alone were normal. Of the subjects examined with anterior and posterior chest leads, 5 were normal, 5 had right ventricular preponderance (Fig. 5 B), as shown by the presence of an inverted QRS in Lead I (in some, together with depression of S-T and inversion of T in Lead III), 5 had left ventricular preponderance of type I (Fig. 5 C), as shown by inversion of QRS in Leads II and III without any notable change in S-T and T in Lead I, and 8 had left ventricular preponderance of type II (Fig. 5 D), as shown by inversion

*Aided by the A. D. Nast Fund for Cardiac Research and the Kuppenheimer Fund.

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Received for publication Nov. 21, 1938.

of QRS in Lead III (or Leads II and III) and depression of S-T in Lead I (and II), and inversion of T in Lead I (and II).

All chest leads were standardized so that 1 millivolt produced a deflection of 1 centimeter. The left leg was chosen for the site of the "indifferent" electrode. Electrode connections were such that relative positivity of the chest electrode gave a downward deflection.* The various points at which chest electrodes were placed, together with abbreviations employed in this report, are shown in Figs. 1 and 2, which are diagrams adapted from published necropsy material.³¹ These figures, as well as Figs. 3 and 4, illustrate the topographic relations between the points used and the structure of the heart.

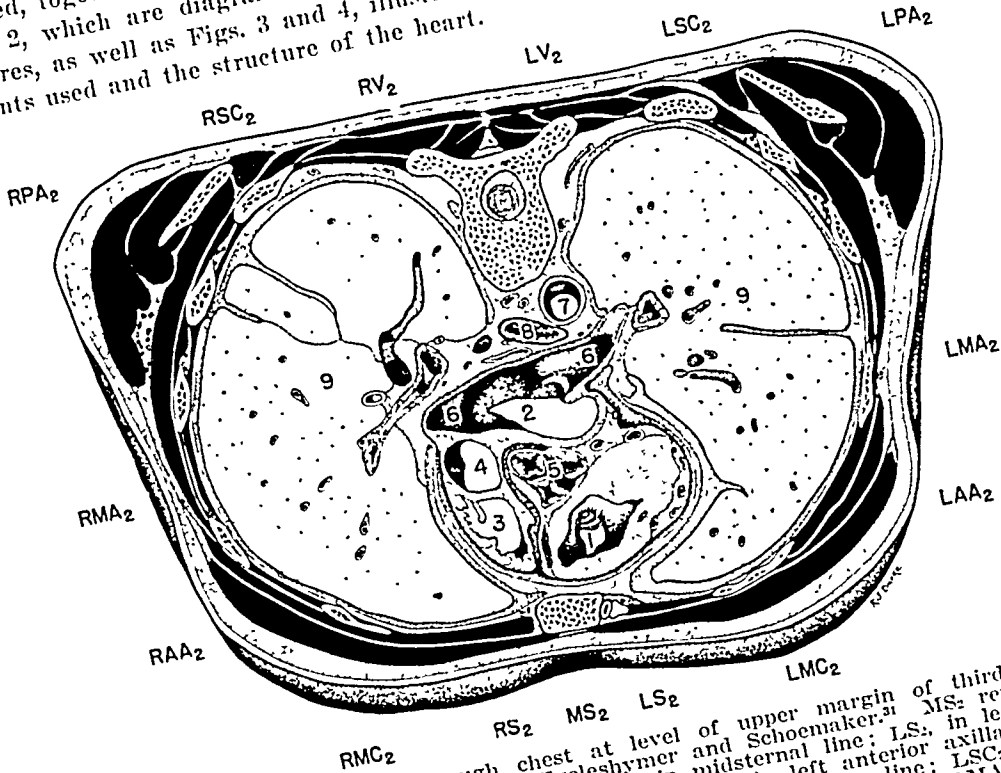


Fig. 1.—Cross section through chest at level of upper margin of third costal cartilage. Modified from sec. 25 of Eycleshymer and Schoemaker.³¹ MS₂ represents point at the level of second intercostal space in midsternal line; LS₂, in left parasternal line; LMC₂, in left midclavicular line; LAA₂, in left anterior axillary line; LMA₂, in left midaxillary line; LPA₂, in left posterior axillary line; LSC₂, in left scapular line; LV₂, in left paravertebral line; RS₂, RMC₂, RAA₂, RPA₂, RSC₂, and RV₂, homologous points on right side. 1 is right ventricle, 2 is left ventricle, 3 is right auricle, 4 is superior vena cava, 5 is aortic valve, 6 is pulmonary vein, 7 is descending thoracic aorta, 8 is esophagus, and 9 is lungs.

DISCUSSION OF RESULTS

Figs. 6 and 7 show typical records from chest leads with electrodes at various points around the chest at the level of the second and fourth intercostal spaces in the normal subject (A), in a patient with right ventricular preponderance (B), and in two patients with the two types of left ventricular preponderance (C and D). These illustrate the general pattern of curves obtained in each of these four categories of patients.

*This is the reverse of the procedure adopted by the American Heart Association. The records were obtained before the report of the American Heart Association was published. The connection we employed makes the chest lead directly comparable to Leads II and III. In Leads II and III relative positivity of the electrode nearer the heart, the right and left arm electrode, respectively, also gives a downward deflection. Lead I should be considered as differing from all of the other leads used in this report, for, unlike Leads II and III, it is really the algebraic sum of electrical effects of electrodes approximately equidistant from the heart. On this account, we feel that the old expression $\text{Lead II} = \text{Lead I} + \text{Lead III}$ should be superseded by $\text{Lead I} = \text{Lead II} - \text{Lead III}$.

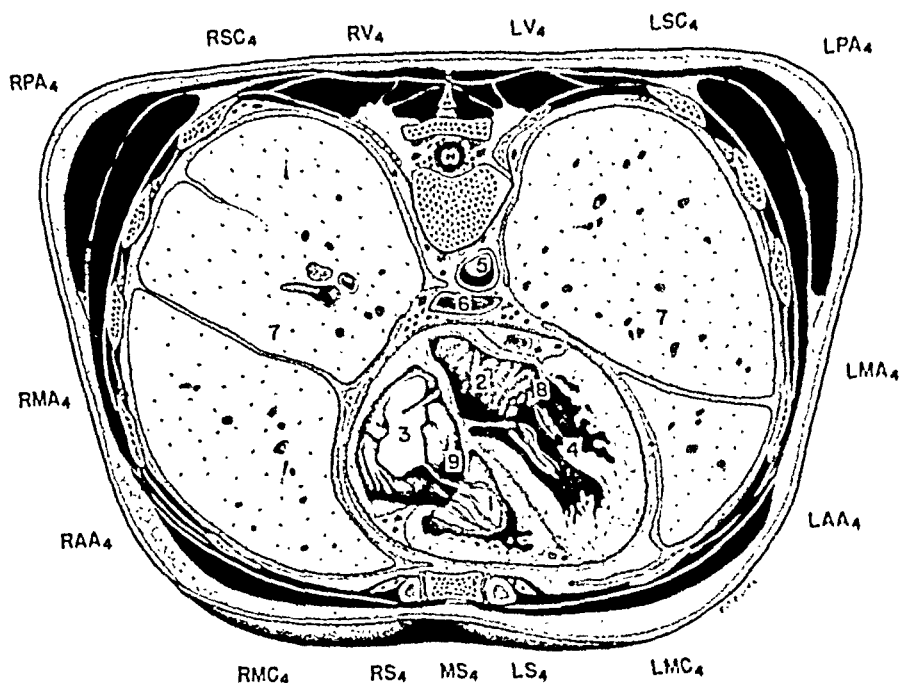


Fig. 2.—Cross section through chest at level of sternal end of fourth costal cartilage. Modified from sec. 26 of Eycleshymer and Schoemaker.²⁰ MS₄, LS₄, LMC₄, LAA₄, LMA₄, LPA₄, LSC₄, LV₄, RS₄, RMC₄, RAA₄, RMA₄, RPA₄, RSC₄, and RV₄ represent points equivalent to MS₂, etc., except that they are at the level of the fourth intercostal space, instead of the second. 1 is the right ventricle, 2 is the left auricle, 3 is the right auricle, 4 is the left ventricle, 5 is the descending thoracic aorta, 6 is the esophagus, 7 is the lung, 8 is the mitral valve, and 9 is the tricuspid valve.

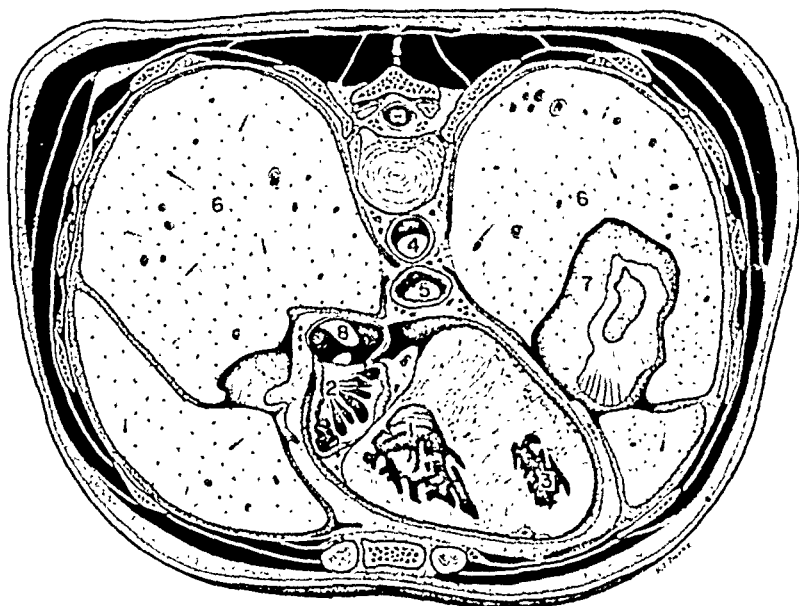


Fig. 3.—Cross section through chest at level of sternal end of fifth costal cartilage. Modified from sec. 27 of Eycleshymer and Schoemaker.²¹ 1 is right ventricle, 2 is left auricle, 3 is left ventricle, 4 is descending thoracic aorta, 5 is esophagus, 6 is lungs, 7 is diaphragm, and 8 is inferior vena cava.

GENERAL PATTERNS

While varying in detail, the following characteristics of the chest leads are common to the 200 subjects studied by us.

(a) There is an orderly pattern of transition from one point on the chest to the next, as regards the sequence and size of the deflections of the QRS complex, the direction of the S-T segment deviation, and the size and direction of the T wave.

(b) The magnitude of the deflections is greater over the anterior chest wall than over the posterior wall.

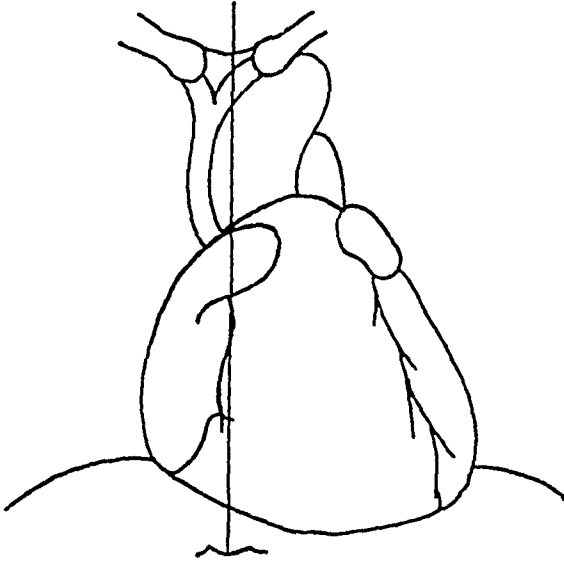


Fig. 4.—Diagram of frontal silhouette of heart.

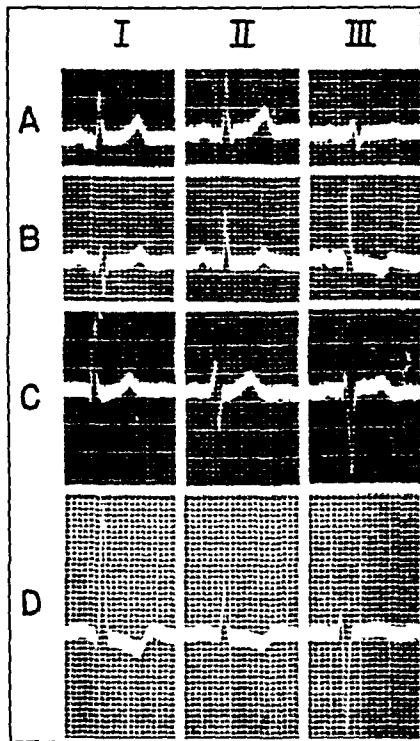


Fig. 5—Segments of standard limb-lead electrocardiograms. *A*, normal subject; *B*, patient with right ventricular preponderance (rheumatic fever with mitral stenosis), and *C* and *D*, two patients with left ventricular preponderance (hypertension). Discussed in text.

(c) At the level of the fourth intercostal space there is a tendency for records from chest points 180° apart to be mirror images of each other.

(d) In going around the chest the QRS complex tends to change from an upright to a diphasic deflection with the first phase directed downward, then to become inverted, then to become diphasic with the first phase directed upward, and, finally, to return to its original contour.

(e) In going around the chest there is a tendency for the T wave to change from an inverted to an upright deflection, and back again. In the transition the T wave may become diphasic.

(f) The S-T segment and T wave usually appear as a single continuous element.

Certain relations were also found between the chest leads and the limb leads, as follows:

(1) Lead LMA₄ is usually the inverse of Lead I. Sometimes, however, LAA₄ is more nearly the inverse of Lead I.

(2) Leads RSC₂ and RPA₂ are almost identical with Lead II.

(3) Leads LSC₂ and LPA₂ are almost identical with Lead III.

FINDINGS IN THE NORMAL HEART

The chest leads shown in *A* of Figs. 6 and 7 are typical for normal young adults. Their general pattern is remarkably constant. Starting in the fourth intercostal space at the left parasternal line, the QRS is diphasic, showing a preliminary downward deflection which increases in depth as the chest electrode moves across the left chest to the anterior axillary line. At the same time, the second upright deflection becomes smaller, then disappears and is replaced by a primary upright phase in the left midaxillary line. On going to the right around the posterior chest wall, the first upright phase increases in height, while the downward deflection decreases and finally disappears in the right midaxillary line. In the right axilla, a preliminary dip reappears and increases in size on going to the right anterior chest.

The S-T segment and the T wave in the left parasternal line are both directed downward. Their deviation from the isoelectric line increases at first as the chest electrode is moved across the chest to the left, but decreases again as the left axilla is approached. In the region of the left scapula both S-T and T are directed upward. The upward deviation waxes as the electrode is moved to the right across the posterior chest, to wane again in the right axilla. The transition from upright to inverted deflections occurs in the region of the sternum. In the midsternal lead a diphasic T wave is found, with the first phase directed downward.*

*The pattern in dogs³² is in general similar to that in man, differing in minor details.

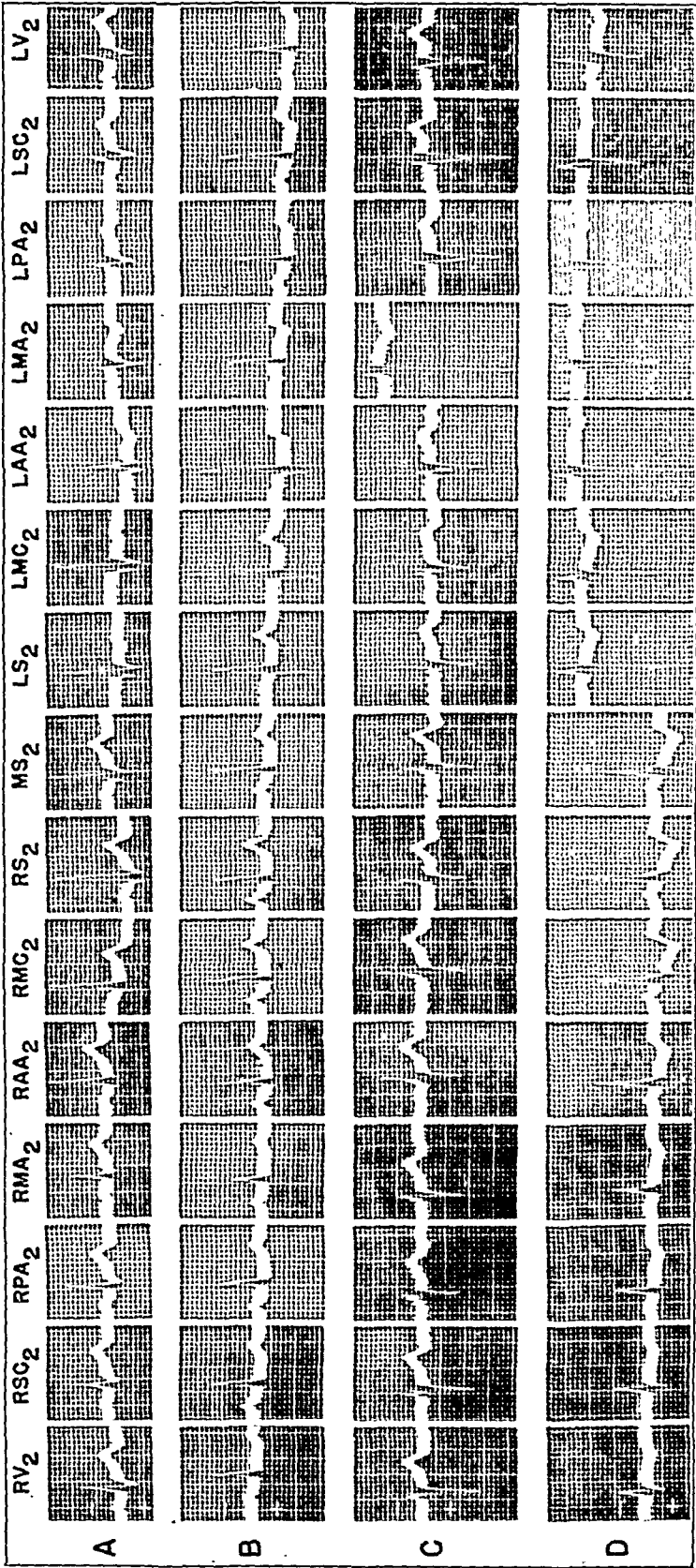


Fig. 6.—Segments of chest lead electrocardiogram in patients A, B, C, and D, referred to in Fig. 5, using chest points indicated in Fig. 1, with the "indifferent" electrode on the left leg. + and - indicate relative positive and negative potential of chest electrode with respect to the left leg. The curves are the inverse mirror image of those obtained by following the recommendation of the American Heart Association Committee's recent report.^{1,5} For this study, the curves as presented are comparable to Leads II and III. Discussed in text.

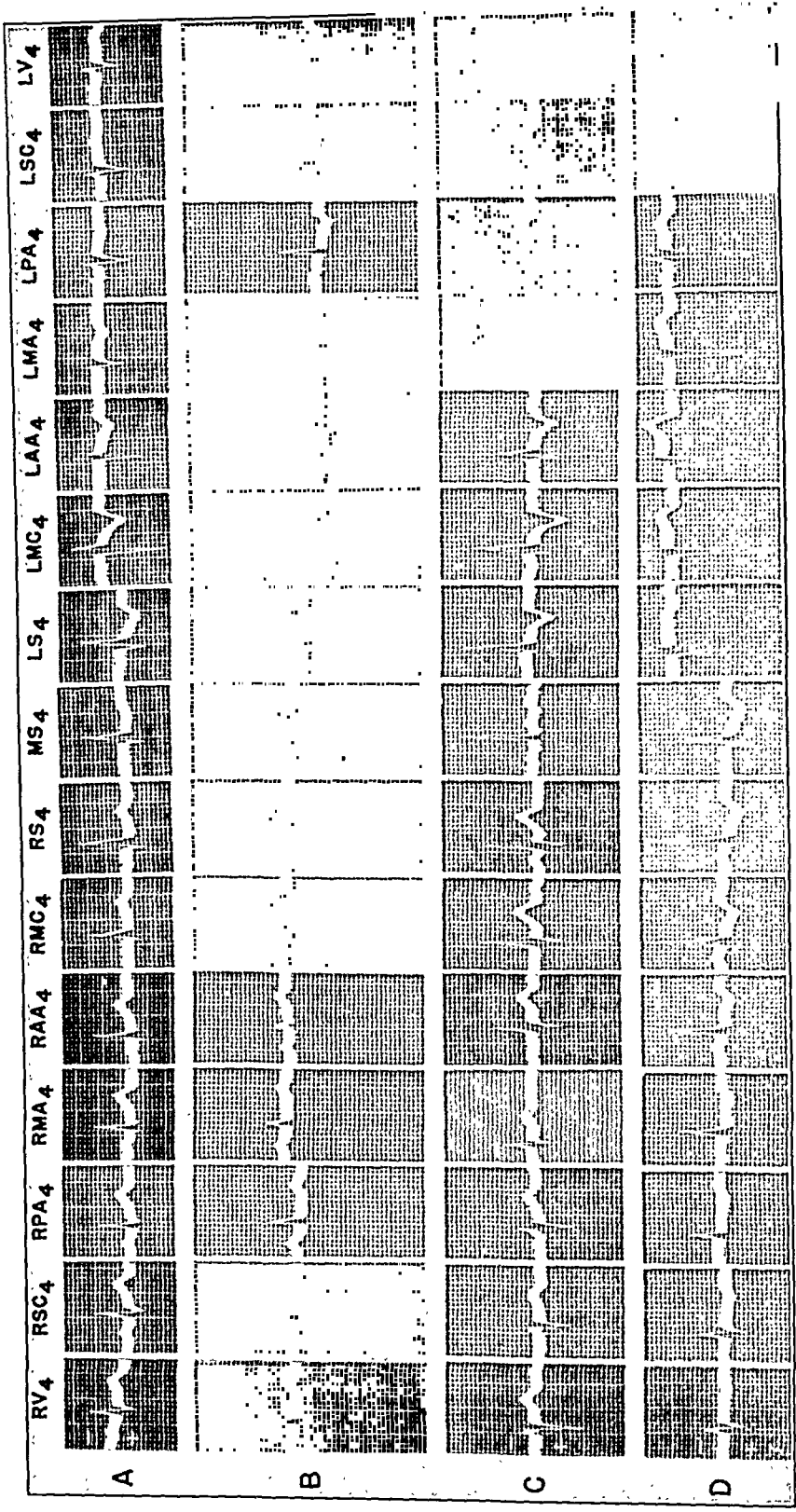


Fig. 7.—Segments of chest lead electrocardiograms in patients A, B, C, and D referred to in Fig. 5, using chest points indicated in Fig. 2, with the "indifferent" electrode on the left leg. Conventions as in Fig. 6. Discussed in text.

A similar pattern exists at the level of the second intercostal space, but the QRS is triphasic and W-shaped over the left anterior chest wall.

When the chest leads and Leads II and III are correlated with the relation of the various electrode positions to the anatomical structure of the heart, the following facts can be established in normals:

1. Near the base of the heart the QRS, S-T, T and P deflections are directed mainly upward.
2. Near the apex of the heart the QRS, S-T, T and P deflections are directed mainly downward.
3. Over the right ventricle and about equidistant from the apex, base, and septum, QRS is diphasic with the first phase directed downward, S-T is depressed, and T is inverted.
4. Over the left ventricle and about equidistant from the apex, base, and septum, QRS is diphasic with the first phase directed upward, S-T is elevated, and T is upright.

FINDINGS IN RIGHT VENTRICULAR PREPONDERANCE

The chest leads in preponderant hypertrophy of the right ventricle (Figs. 6 B and 7 B) differ considerably from the normal, as follows:

1. The QRS complex over the area of absolute cardiac dullness is considerably greater than normal, and the second upright phase is as tall, or taller, than the first downward phase.
2. No entirely inverted QRS, or diphasic QRS with the first phase directed upward, is seen anywhere.
3. The smallest QRS at the level of the fourth intercostal space is in the right anterior axillary line. The increase in the magnitude of QRS on going over the anterior chest to the left is striking.
4. Both the upright and inverted T waves show a greater amplitude than normal in the area of absolute cardiac dullness.
5. The T wave is upright over the entire right chest anteriorly, so that the transition from upright to inverted T waves is shifted to the left. It occurs between the left midclavicular and anterior axillary lines.
6. The other transition, from inverted to upright T waves, is shifted to the right. It occurs posteriorly between the left and right vertebral lines; at this point the T wave is diphasic.

FINDINGS IN LEFT VENTRICULAR PREPONDERANCE

Two types of limb lead electrocardiograms can be distinguished in cases of preponderant hypertrophy of the left ventricle. In one type, QRS is directed downward in Leads II and III, but the T wave remains upright in all three leads. In the other, QRS is directed downward either in Lead III alone or in both Leads II and III; in Leads I and II the T wave becomes inverted and the S-T segment becomes depressed. The latter type resembles the common type of bundle branch block, but the

duration of QRS is less than 0.12 sec. The illustrated curves (Figs. 5 C and D, and 6 and 7 C and D) are typical, but intermediate forms are also seen.

In the first type of left ventricular preponderance (Figs. 6 C and 7 C) the following chief differences from the normal are found:

1. The QRS complex is larger than normal over most of the chest, especially in the left midaxillary and posterior axillary lines. The QRS complex is largest in LMA_1 , whereas in right ventricular preponderance the maximum is at MS_4 .

2. The points at which upright, inverted, and diphasic QRS complexes appear at the level of the fourth intercostal space are shifted to the left on the anterior surface of the chest and to the right on the posterior surface. At the level of the second intercostal space the QRS complex is diphasic, with the first phase directed upward at all points.

3. The direction of the T wave and the S-T segment at the level of the fourth intercostal space is generally the same as in the normal, but the S-T deviations and T deflections are larger. At the level of the second intercostal space the T wave is upright at all points except at LMA_2 .

The second type of left ventricular preponderance (Figs. 6 D and 7 D) presents the following chief differences from the normal:

1. The QRS complex is larger than normal over the whole chest except the right posterior portion. Especially striking is the increase in the region between the left midclavicular line and the left midaxillary line. This is to the right of the region of maximum QRS excursion in the first form of left ventricular preponderance, and to the left of that in right ventricular preponderance.

2. The transition from an upright to an inverted QRS complex over the anterior chest wall is more abrupt than normal, occurring between RS_4 and LS_4 . The QRS complexes at the level of the second intercostal space differ from those in the first type of left ventricular preponderance in that they are upright, not diphasic, over the right anterior and posterior chest wall.

3. Unlike in the first form, the T wave and S-T segment in the second type of left ventricular preponderance are the inverted mirror images of their normal appearances in all chest leads studied.

THE DIAGNOSTIC SIGNIFICANCE OF CHEST LEADS IN PREPONDERANT HYPERTROPHY

The above characteristics of the various chest leads depict the chief deviations from normal in preponderant hypertrophy of the right and left ventricles. Variations which occur from subject to subject can be explained by differences in chest contour, in position of the heart, in the amount of damage to the conduction system and heart muscle, in the degree of hypertrophy and dilatation of the chamber chiefly involved, and in the amount of dilatation and hypertrophy of the other heart chambers, especially the other ventricle.

The changes in the chest leads are probably as characteristic as the changes which are utilized to recognize right and left ventricular preponderance in the standard limb leads. The diagnostic significance of the ratio of the magnitude of QRS over the sternum and that over the left axilla has already been reported by other observers,^{6, 10, 11, 29}

MEANING OF CHEST LEADS IN TERMS OF THE ELECTRICAL FIELD THEORY

(a) *The Source of the Electrical Field.*—As outlined previously,¹² the electrical manifestations of the heartbeat form a three-dimensional electrical field. The characteristics of this field depend on (a) the conductivity and shape of the medium in which the electrical currents flow, and (b) the nature of the current source. In a previous communication¹² evidence was presented to show that the electrical medium has the shape of the torso of the body; the extremities, head, and neck have very little influence. This medium is composed of various electrical conductors, their arrangement being complicated by the eccentric position of the heart. The different qualities of these electrical conductors and consequently their different influence on the electrical field of the heart have been demonstrated in the dog whose chest is closed³² by a method similar to that used for the dog whose chest is open.⁴³ A new concept¹² based on these experimental facts has served as a convenient working hypothesis in clinical electrocardiography.⁴⁴

More important than the medium is the source of the electrical field. When the heart is in situ, it has been established³³ that small batteries of closely adjacent positive and negative electrical elements appear within the heart during the periods of activation and recovery wherever regions in different states of activity and recovery are in juxtaposition. These batteries lie at the junction between relatively active and inactive regions, and between the relatively recovered and unrecovered regions. They are the source of the electrical field.

It is desirable to define the pattern of activation and recovery in the heart. The impulse travels down the common bundle and its branches, and then along the Purkinje network, which, as recent work has shown, extends into the myocardium itself.³⁴ The batteries can therefore be imagined to start at a point approximately at the junction of the upper and middle thirds of the septum, halfway between the anterior and posterior interventricular grooves, where the Purkinje fibers begin to flare out. From this point they spread in a radial fashion in the septum, assuming that there is fairly uniform spread through the Purkinje network. The dimensions of the septum are such that the battery front reaches a point on the anterior and a point on the posterior interventricular groove ahead of other parts of the surface of the heart. From these two points four battery fronts travel over the outer walls of the ventricles, still keeping the more or less circular outline, with the center of radiation at the point in the septum previously mentioned. Since the

left ventricle is normally larger and thicker than the right, the battery fronts spreading over its walls dominate those spreading over the right ventricle.

It must be borne in mind that activation of a single region occupies several hundredths of a second, the duration of the sharply ascending portion of the monophasic action curve of a single region. This time span required for completing the activation of each point of the ventricles alters the location and dimensions of the batteries during the invasion of the ventricles.

Recovery begins soon after invasion and occupies most of the electrical systole, as demonstrated by the early decline of the monophasic action curve. The relatively long period of recovery establishes a second battery group, which occupies the second part of ventricular activity. As the slope of the monophasic curve indicates, the rate of recovery is slow at the beginning, increases gradually, and abruptly slows at the end. It never attains the speed of the activation process. The strength of the second battery group changes with the rate of recovery, quickly disappearing when recovery is completed. Completion of recovery is not synchronous in all parts of the ventricles, and this asynchronism is not determined entirely by the pattern of invasion.

Thus, two complex batteries appear in succession during ventricular activity, one occupying the invasion period and the other the entire recovery period. The first is a large battery of varying intensity; the second is smaller, attains its maximum slowly, and then fades out more abruptly than it developed. These two successive batteries are complex as regards voltage, position, shape, and area of their poles, and these characteristics change from moment to moment.

(b) *The Determination of the Surface Field in a Horizontal Plane at the Level of the Sternal End of the Fourth Intercostal Space.*—No direct information is available concerning the electrical field within the human body. But the field on the surface of the body can be mapped out from moment to moment, and can be defined by the following qualities: (1) the position of the zero potential lines, (2) the location and extent of the positive and negative fields, and (3) the concentration of potential lines in various regions of the surface.

In this report we present data derived from the exploration of a horizontal plane at the sternal level of the fourth intercostal space, as described above. The surface distribution of potential in this plane was determined at four points in the heart cycle, namely, 0.03, 0.07, 0.24, and 0.32 second after the beginning of the QRS complex. The first two points occur during the first and last thirds of the QRS complex; the last two points are situated on the first and second halves of the T wave. Changes of the surface field between these four points can be readily surmised. The outline of these four surface fields is somewhat inaccurate, since the points selected in the various chest leads are only

approximately homologous, and because the leg electrode is not quite "indifferent." Nevertheless, this approach seems accurate enough to show the genesis of the electrocardiogram obtained at various points on the chest. The relative potential of the chest electrodes at each of the four moments selected is illustrated for the normal heart (Fig. 8 A, B, C, and D) and for the different types of preponderant ventricular hypertrophy (Figs. 9, 10, and 11). The numerals on the chart represent multiples of 0.1 millivolt. In each of the sixteen diagrams the positions of the zero potentials are indicated, and lines are drawn to show the spacing on the surface of potential lines differing from each other by 0.1 millivolt. The points of maximum positive and negative potential are marked + and -, respectively.

1. THE SURFACE FIELD IN THE NORMAL HEART

The electrical field on the surface of the chest during the first stage of activation of the ventricles (Fig. 8 A) has a greater concentration of positive potential lines and a greater maximum positive potential than the negative field. The maximum positive potential is in the regions of LMC_4 , the maximum negative potential, in the region of RPA_4 and RSC_4 . The line of zero potential is between RAA_4 and RMC_4 and between LPA_4 and LMA_4 . During the latter part of the period of activation (Fig. 8 B), the field rotates about 90° in a counterclockwise direction when viewed from above. The maximum positive potential now lies in the region of LPA_4 , and the maximum negative potential in the region of MS_4 . The zero potential lines have shifted to LAA_4 , and between RPA_4 and RMA_4 . During invasion, the surface field waxes at first, rotates in a counterclockwise direction about 90° , and then wanes. The surface field during recovery is never as strong as that developed during activation and does not rotate much; the location of the maximum positive and negative surface potentials and of the lines of zero potential is similar to that during the first stage of activation.

Despite the complexity of the batteries occurring during electrical systole and the heterogeneity of the electrical conductors adjacent to the heart, the pattern in this plane can be readily correlated with the patterns of activation and recovery outlined above, and with the topographic anatomy of the heart. Figs. 1 to 4 show (1) that the heart is closer to the front than to other parts of the chest surface, and that this frontal surface is formed chiefly by the right ventricle; (2) that the right and left ventricles share the diaphragmatic surface about equally; (3) that the ventricular septum is almost entirely to the left of the midline; and (4) that it runs obliquely downward from right to left, forming an angle of about 45° with the midline.

During the first part of activation, the batteries start in the upper third of the septum midway between the anterior and posterior interventricular grooves, and, as they move anteriorly, downward, and to the left, they wax in strength as the extent of the area of junction between

active and inactive regions grows. By virtue of the spread of activation through the septum, the positive pole, in as yet inactivated tissue, lies, in general, more toward the apex of the heart and the anterior and lower part of the trunk than the negative pole in activated tissue. This accounts for the distribution of the surface field. The rotation of the field at the time when the potential strength at the surface of the chest is largest coincides with the spread of activation from the septum to the outer walls of the ventricles. The batteries over the right ventricle are directed opposite to those in the left, and hence tend to neutralize somewhat the surface field produced by the latter. But since the left ventricle normally is greater in area and thickness, the batteries over this ventricle dominate those of the right. The

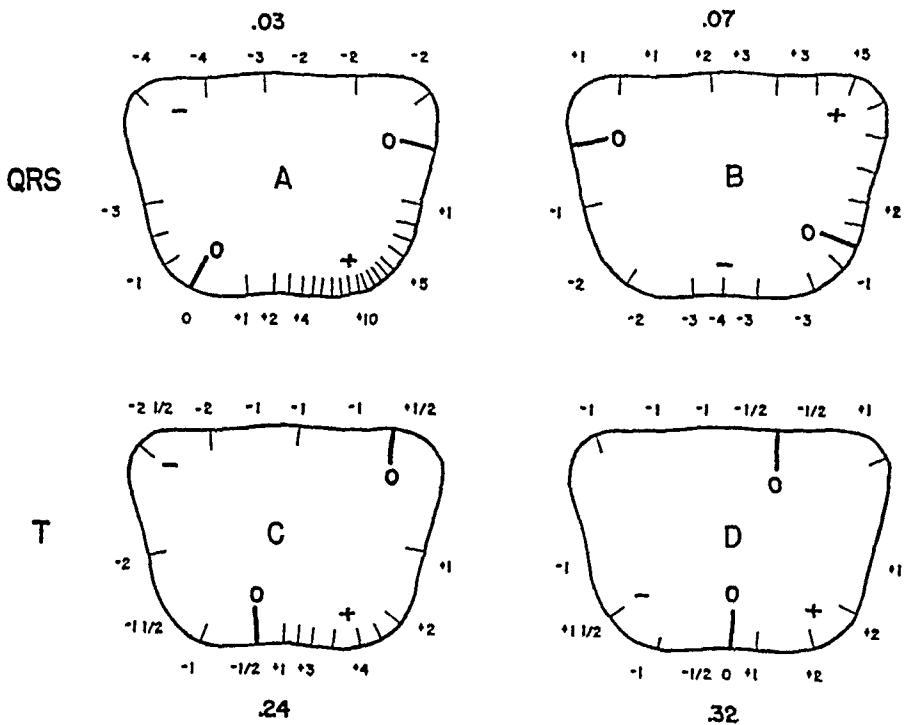


Fig. 8.—Cross-section diagrams A, B, C, and D represent the distribution of surface potential in normal subject at level of sternal end of fourth intercostal space 0.03, 0.07, 0.24, and 0.32 sec., respectively, after onset of QRS. Potential values are expressed in terms relative to leg potential, in multiples of 0.1 of a millivolt. Discussed in text.

batteries in the anterior and posterior walls of the left ventricle spread laterally toward the posterior axillary line. Therefore, the positive pole of the major battery lies, at this time, in general, lateral and somewhat posterior to the negative pole. This represents a rotation of about 90° in a plane approximately parallel to the horizontal plane depicted. It corresponds to the field rotation noted at this time. As the activation process is completed, the batteries fade out.

The orientation of the surface field during the recovery process, with maximum positive potential to the left and maximum negative potential to the right, suggests that the base and lateral walls of the right ventricle

lag behind the apex and left ventricle in their recovery. This is in accord with data on the relative duration of the mechanical systole in the two ventricles,³⁵ and again emphasizes how little the pattern of recovery normally depends on the pattern of invasion.³⁶

2. THE SURFACE FIELD IN RIGHT VENTRICULAR PREPONDERANCE

The pattern of the surface field differs considerably from the normal (compare Figs. 8 and 9), as follows:

Activation.—The field in the first part of activation is oriented similar to the normal as regards the location of the lines of zero potential and of the maximum negative and positive fields. However, the concentration of positive potential lines is much greater on the anterior surface, the maximum potential is considerably greater, and the area of maximum potential is displaced to the left to MS_1 . At the same time the maximum negative potential is somewhat smaller. In the stage of activation, when the field rotates the positive field disappears from the horizontal plane depicted, and the maximum negative potential comes to lie near the point of maximum positive potential. This indicates that the field has rotated markedly in a plane located at a large angle from the horizontal, and that the positive field must be located somewhere in the lower chest, probably posteriorly. In the second stage of invasion, the concentration of the potential lines over the front of the chest, as well as of the maximum negative potential, remains much greater than normal.

Recovery.—While the maximum positive potential lies in the normal region, the maximum negative potential is displaced in a counterclockwise direction towards MS_4 , and comes to lie close to the point of maximum positive potential. The concentration of the potential lines is decreased over the right posterior quadrant and increased over the left anterior quadrant. There is, furthermore, little rotation of the field during recovery.

Anatomic Correlation.—These changes in the field can be correlated with the changes in the pattern of invasion and retreat which accompany hypertrophy of the right ventricle. These changes are partly due to positional changes of the heart accompanying this condition, and partly to the effect of the increased mass of the right ventricle. In hypertrophy of the right ventricle, this chamber moves downward on the diaphragm and forward to gain closer contact with the front of the chest. The vertical height of the right ventricle is increased, and the area presenting itself anteriorly exceeds that on the diaphragm. The anterior interventricular groove is displaced to the left, and the septum bulges less into the right ventricle. The septum also lies more nearly vertical, losing some of its tilt to the left.

As activation begins, the batteries at equivalent moments during the spread through the septum come closer to the anterior chest wall, accounting for the increased concentration of potential lines here and the

decreased concentration posteriorly. The displacement of the septum and the greater mass of the right ventricle alter the summation of the batteries over the outer walls of the two ventricles during the second stage of invasion. The batteries in the outer wall of the right ventricle are more dominant because the enlarged right ventricle is closer to the front of the chest and occupies more of its surface area. These circumstances bring about an abnormal angulation of the field. The orientation of the field in the second phase of activation indicates that the spread which dominates is the one from the anterior surface backward, to the right, and downward. This is the manner in which the activation can be imagined to spread over the walls of the hypertrophied right ventricle, presenting itself beneath the anterior chest wall. The field distribution during recovery also fits the view that recovery in the hypertrophied right ventricle and the base of the heart lags behind that in the apex and left ventricle.

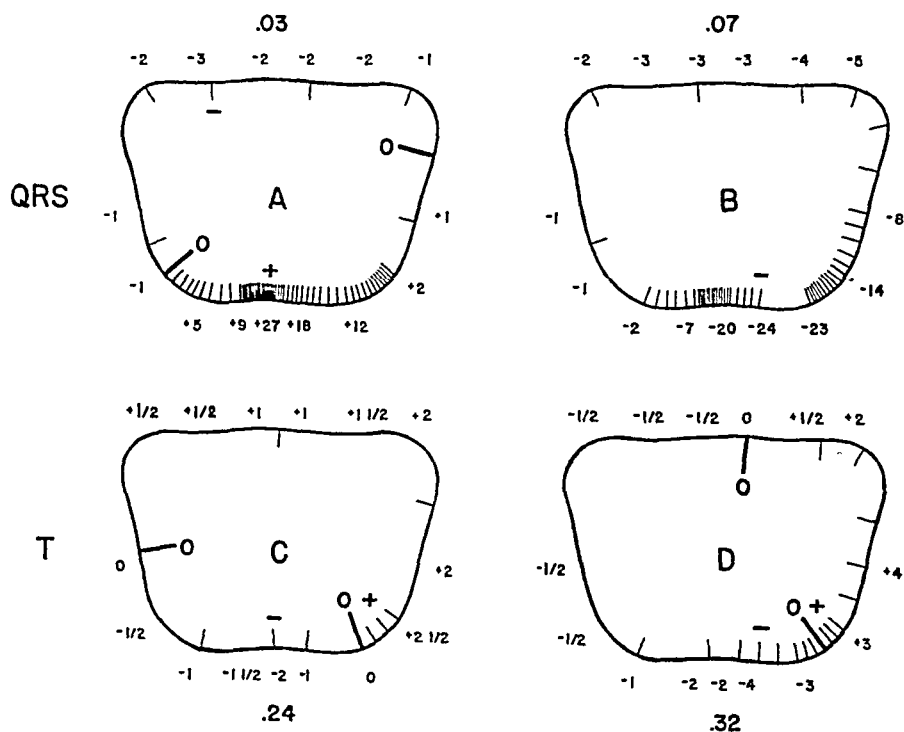


Fig. 9.—Cross-section diagrams A, B, C, and D represent the distribution of surface potential obtained as in Fig. 8 from subject with right ventricular preponderance. Discussed in text.

3. THE SURFACE FIELD IN LEFT VENTRICULAR PREPONDERANCE

A. *First Type*.—In the first type of left ventricular preponderance (Figs. 8 and 10) the chief differences from the normal are the following:

(a) During the first stage of activation the lines of zero potential are closer together than normal, being located at LMC_4 and LMA_4 . The positive field is smaller in area and weaker than normal, while the negative field is larger and stronger. The greatest concentration of potential

lines is located over the sternum, instead of the anterior axilla (A of Figs. 8 and 10).

(b) The rotation of the field is less than normal (about 30°), although in the same direction.

(c) In the second stage of activation the zero lines are still close together, the first now being at LAA_4 and the second close to RMC_4 . The positive field has grown greatly in area and strength while the negative field has shrunk in area and strength. The greatest concentration of potential lines is now located in the anterior part of the left axilla, and their strength over the entire chest surface is greatly in excess of the normal.

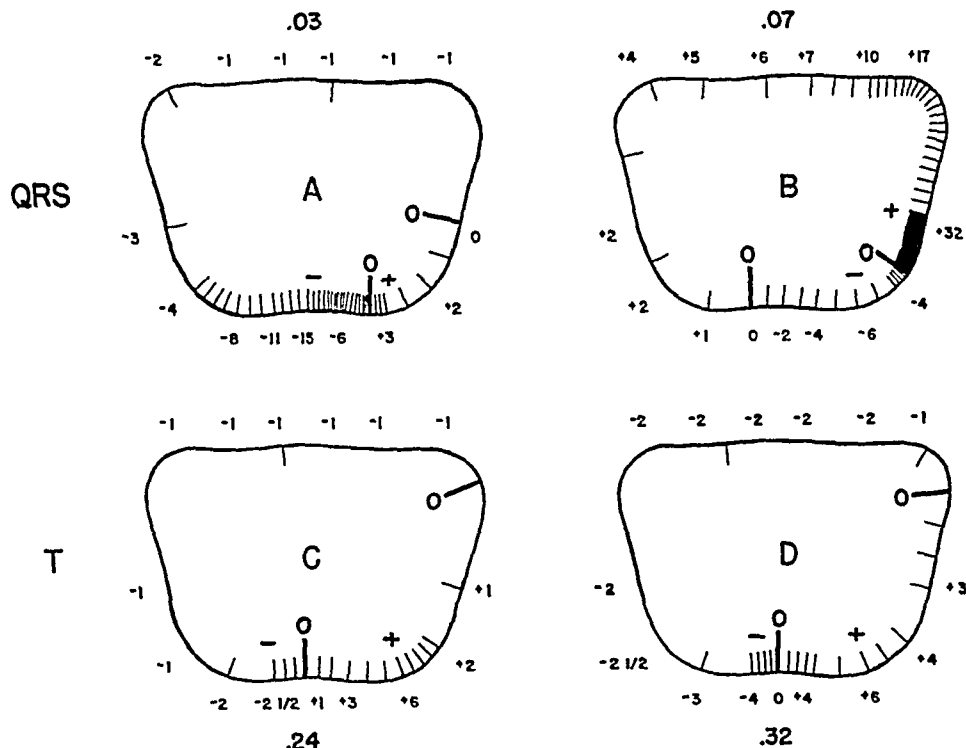


Fig. 10.—Cross-section diagrams A, B, C, and D represent the distribution of surface potential obtained as in Fig. 8, from subject with first type of left ventricular preponderance. Discussed in text.

(d) During recovery, the field is more concentrated anteriorly and laterally than normal, and the maximum negative potential lies closer to the maximum positive potential. There is practically no rotation of the surface field during the recovery period, and the general orientation is similar to the normal.

B. Second Type.—In the second type of left ventricular preponderance, the surface field resembles the normal field more closely during activation, but differs entirely from the normal during recovery.

The chief differences between this second type of left ventricular hypertrophy and the normal are the following (Figs. 8 and 11):

(a) In the first stage of activation the lines of zero potential, the maximum positive potential, and the maximum negative potential are

displaced in a counterclockwise direction from their normal positions. The strength of the positive and negative fields and the concentration of potential lines are increased, particularly over the left anterior quadrant.

(b) The rotation of the field, as in the first type of left ventricular preponderance, is less than normal (about 30°) and in the same direction.

(c) In the second phase of activation, the concentration and magnitude of the positive and negative fields are greater than normal.

(d) During recovery, the location of the positive and negative fields is almost the reverse of the normal.

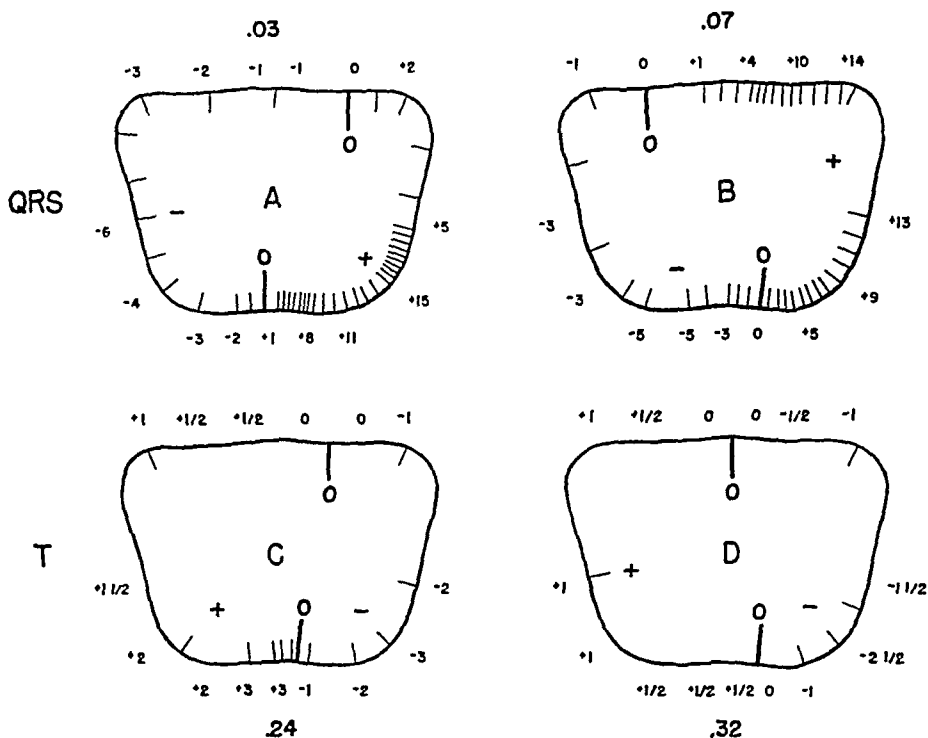


Fig. 11.—Cross-section diagrams A, B, C, and D represent the distribution of surface potential obtained as in Fig. 8, from subject with second type of left ventricular preponderance. Discussed in text.

C. Anatomic Correlation.—These changes in the surface field in left ventricular preponderance fit the following known changes of the heart in this condition: the area and mass of the left ventricle are increased; the heart elongates to the left and downward and rotates counterclockwise on its long axis, so that the left ventricle comes in more intimate contact with the paravertebral muscle mass; the anterior interventricular groove and the right ventricle are displaced to the right; and the septum runs more nearly vertically and bulges much more than normally into the right ventricle, and so lies closer to the anterior chest wall.

With activation beginning in the septum, the fact that it lies closer to the anterior chest wall accounts for the greater field strength here during

the first phase of activation. The shift in the septum explains the displacement of the field in a counterclockwise direction during this phase of activation. Since under these circumstances the battery front spreads from left to right in the septum as well as over the outer wall of the hypertrophied left ventricle, the degree of rotation of the field will be less than normal during the passage of the battery front from the septum to the outer wall of the ventricles. The closer contact of the heart with the chest wall over the left anterior and axillary regions explains the greater magnitude and concentration of the potentials over this region.

The orientation of the field during recovery is the chief distinguishing characteristic between the two types of left ventricular preponderance. In the first, the pattern of recovery is like the normal, indicating that recovery lags in the base and right ventricle behind the apex and left ventricle. The complete reversal of the field from normal during recovery in the second type of left ventricular preponderance is evidence that, probably because of the great hypertrophy of the left ventricle and advanced heart muscle changes, there is a lag of recovery in the left ventricle, i.e., the pattern of recovery is set by the pattern of activation.

A CONSIDERATION OF THE VARIOUS THEORIES OF THE SURFACE FIELD

The surface fields shown in Figs. 8 to 11 are asymmetric and show peculiar concentrations and spreads of potential lines. Obviously, these fields cannot be produced by a single bipole changing its voltage and direction from moment to moment, nor even by a pair of simultaneous bipoles. However, these results agree with our amplification^{12, 14} of Waller's proposition, namely, that the field is produced in a heterogeneous conducting medium by a complex battery which changes its pattern, voltage, position, and distance between poles in a complex way from moment to moment. We regard the concept of Eyster and his collaborators^{37, 38, 39} of two bipoles moving simultaneously and independently during activation of the heart, and another pair during recovery, as an oversimplification. This criticism applies even more to the ideas of Groedel and his associates.¹¹ The three-dimensional vector diagram which Schellong and his associates,⁴⁰ among others, have recently utilized, does not give the complete picture of what is happening, even though it may offer diagnostic possibilities.

Our results do not support the view of Wilson and his collaborators⁴¹ that the anterior chest leads depict, preferentially, events in regions of the heart beneath the chest electrode. The distance from the surface of the heart to the anterior chest wall is sufficient to minimize the effect of any one small area of the heart. The sharp reversal in direction of QRS and its orderly time pattern on the anterior chest also fit our concept. If leads from the anterior chest were "semidirect," as claimed by Wilson, et al.,⁴¹ then esophageal leads close to the left ventricle, pos-

teriorly, should also be "semidirect," and the record from the esophageal lead should resemble in contour that obtained over the anterior wall of the chest and that from a unipolar lead directly from the heart's surface. This is not the case.^{32, 42} With the esophageal lead, the QRS phase sequence is the reverse of that in unipolar leads made directly from the heart's surface and of that in anterior chest wall leads. Except for their larger magnitude, esophageal leads⁴² resemble leads from the posterior chest wall. Experience gained with the esophageal lead is in accord with our field theory. It follows that the data derived from chest leads by Wilson's school cannot be accepted as indicating the sequence of activation of the ventricles. The sequences measured by Wilson appear to represent merely the time at which the various points on the chest enter the negative part of the surface field as it rotates during the passage of activation from the septum to the outer walls of the ventricles. Hence, the evidence based on chest leads advanced by Wilson and his collaborators on the order of activation of the two ventricles in intraventricular block must be held sub judice.

THE VALUE OF MULTIPLE CHEST LEADS

We have presented evidence which supports the theory that the time record of the various points on the upper chest, including the right and left arms (Leads II and III), represents the fluctuation of the electrical field in a heterogeneous conducting medium, generated by the complex, constantly changing battery occurring in the heart during ventricular activity. The patterns developed can be correlated with the anatomic and functional experimental evidence in both normal and hypertrophied hearts.

Further investigation may show that multiple chest leads give a better index of ventricular hypertrophy than do the standard limb leads. This is suggested by the fact that definite patterns can be obtained from multiple chest leads which lend themselves to analysis on a deductive physiologic, instead of an empirical, basis. A relatively small number of chest leads, labelled CF_1 , CF_2 , CF_3 , CF_4 , CF_5 , and CF_6 in the recent report of the American Heart Association,⁵ may be sufficient to obtain information for clinical purposes.

Further studies of multiple chest leads in other conditions will be presented by us in subsequent reports.

SUMMARY

1. Electrocardiograms were obtained from various points on the chest wall in normal subjects and in the patients with right and left preponderant ventricular hypertrophy.
2. These records were used to reconstruct and analyze the changing surface electrical field of the heart during the phases of electrical systole.
3. Electrocardiograms from chest leads were interpreted as potential fluctuations in a heterogeneous conducting medium of an electrical field, generated by a series of complex, constantly changing batteries.

4. These fluctuations follow a definite pattern: (1) a period of waxing potential during activation of the septum, (2) a period of rapid rotation of the field as activation spreads from the septum to the outer wall of the ventricles, (3) a period of waning as activation of the outer ventricular walls is completed, and (4) a waxing and waning of potential, with slight rotation, during recovery.

5. The pattern in preponderant hypertrophy of the ventricles differs considerably from the normal. The differences can readily be correlated with changes in the spread of the batteries and in the arrangement of the conducting medium which are known to occur under such conditions. These patterns were remarkably constant and characteristic in the types of hearts studied.

6. The constancy of these patterns and their new interpretation lend a new significance to multiple chest leads.

We are indebted to the several internes and Heart Station technicians for assistance in obtaining the records, and to Mr. Russell Burke for making the drawings.

REFERENCES

1. Wolferth, C. C., and Wood, F. C.: Electrocardiographic Diagnosis of Coronary Occlusion by Use of Chest Leads, *Am. J. Med. Sci.* 183: 30, 1932.
2. Wilson, F. N., Macleod, A. G., Barker, P. S., Johnston, F. D., and Klosternmeyer, L. L.: The Electrocardiogram in Myocardial Infarction With Particular Reference to the Initial Deflections of the Ventricular Complex, *Heart* 16: 155, 1933.
3. Roth, Irving R.: On the Use of Chest Leads in Clinical Electrocardiography, *AM. HEART J.* 10: 798, 1935.
4. Committee of the American Heart Association on Chest Leads—Standardization of Precordial Leads, *J. A. M. A.* 110: 395, 1938.
5. Standardization of Precordial Leads—Supplementary Report, *Ibid.* 110: 681, 1938.
6. Wilson, F. N., Johnston, F. D., Macleod, A. G., and Barker, P. S.: Electrocardiograms That Represent the Potential Variations of a Single Electrode, *AM. HEART J.* 9: 447, 1934.
7. Larsen, K. H.: Some Remarks on the Technique in Clinical Electrocardiography With Precordial Derivation, *AM. HEART J.* 14: 1, 1937.
8. Larsen, K. H., and Warburg, E. J.: A Rational Principle for the Connections of the Leads of the Electrocardiograph in Clinical Electrocardiography With Precordial Derivation, *AM. HEART J.* 14: 7, 1937.
9. Gilson, A. S., and Bishop, G. H.: The Effect of Remote Leads Upon the Form of the Recorded Electrocardiogram, *Am. J. Physiol.* 118: 743, 1937.
10. Holzman, M.: Klinische Erfahrungen mit elektrokardiographischen Brustwandableitungen, *Archiv für Kreislaufforschung*, Band I, Heft 1-6, 1937.
11. Groedel, Franz M.: Das Extremitäten-, Thorax- und Partial-Elektrokardiogramm des Menschen. Eine vergleichende Studie. 2 vol. Dresden und Leipzig, 1934, Theodor Steinkopff.
12. Katz, L. N., in collaboration with A. Bohning, I. Gutman, K. Jochim, H. Korey, F. Oeko, and M. Robinow: Concerning a New Concept of the Genesis of the Electrocardiogram, *AM. HEART J.* 13: 17, 1937.
13. Wood, F. C., and Wolferth, C. C.: An Electrocardiographic Study of Experimental Coronary Occlusion: The Inadequacy of the Three Conventional Leads in Recording Certain Characteristic Changes in Action Current, *J. Clin. Investigation* 11: 815, 1932.
14. Wood, F. C., Bellet, S., McMillan, T. M., and Wolferth, C. C.: Electrocardiographic Study of Coronary Occlusion: Further Observations on the Use of Chest Leads, *Arch. Int. Med.* 52: 752, 1933.
15. Wood, F. C., and Wolferth, C. C.: Huge T-Waves in Precordial Leads in Cardiac Infarction, *AM. HEART J.* 9: 706, 1934.

16. Levine, Louis: Chest Leads in Coronary Occlusion, *M. J. and Rec.* 136: 421, 1932.
17. Hoffman, A. M., and Delong, E.: Standardization of Chest Leads and Their Value in Coronary Thrombosis and Myocardial Damage, *Arch. Int. Med.* 51: 947, 1933.
18. Katz, L. N., and Kissin, M.: A Study of Lead IV, *AM. HEART J.* 8: 595, 1933.
19. Bellet, S., and Johnston, C. G.: The Effect of Coronary Occlusion Upon the Initial Phase of the Ventricular Complex in Precordial Leads, *J. Clin. Investigation* 13: 725, 1934.
20. Feinstein, Marcus A., and Lieberman, Abraham: Characteristic Serial Changes in the Fourth Lead After Acute Coronary Thrombosis, *AM. HEART J.* 14: 69, 1937.
21. Bohning, A., and Katz, L. N.: Four Lead Electrocardiogram in Cases of Recent Coronary Occlusion, *Arch. Int. Med.* 61: 241 and 519, 1938.
22. Lieberman, A., and Liberson, F.: The Value of the Posterior-Anterior Chest Leads in Cardiac Diagnosis, *Ann. Int. Med.* 6: 1315, 1933.
23. Goldbloom, A. A.: Clinical Evaluation of Lead IV (Chest Leads). A Survey of Lead IV in Ambulatory Cases of Coronary Artery Disease and Acute Coronary Occlusion, *Am. J. Med. Sci.* 187: 489, 1934.
24. Bohning, A., and Katz, L. N.: The Four Lead Electrocardiogram in Coronary Sclerosis, *Am. J. Med. Sci.* 189: 833, 1935.
25. Levy, R. L., and Bruenn, H. G.: The Precordial Lead of the Electrocardiogram (Lead IV) as an Aid in the Recognition of Active Carditis in Rheumatic Fever, *AM. HEART J.* 10: 881, 1935.
26. Levine, H. D., and Levine, S. A.: An Electrocardiographic Study of Lead IV With Special Reference to the Findings in Angina Pectoris, *Am. J. Med. Sci.* 191: 98, 1936.
27. Van Nieuwenhuizen, C. L. C., and Hartog, H. A. P.: Chest Leads in Electrocardiography, *Arch. Int. Med.* 59: 448, 1937.
28. Van Nieuwenhuizen, C. L. C., and Hartog, H. A. P.: The Electrocardiogram in Hypertension With Special Reference to Lead IV, *AM. HEART J.* 13: 308, 1937.
29. Roth, Irving R.: Chest Lead Tracings in Arterial Hypertension With Cardiac Enlargement, *AM. HEART J.* 14: 155, 1937.
30. Ekey, P., and Fröhlich, R.: Zur Frage der unipolaren Ableitung des Electrocardiogramms, *Arch. f. Kreislaufforschung* 2: 349, 1938.
31. Eycleshymer, A. C., and Schoemaker, D. M.: A Cross Section Anatomy, New York & London, 1911, Appleton and Co.
32. Lindner, E., and Katz, L. N.: *Am. J. Physiol.* (in press).
33. Craib, W. H.: The Electrocardiogram. Special Report Series No. 147, Medical Research Council, 1930.
34. Abramson, D. I., and Jochim, K.: The Spread of the Impulse in the Mammalian Ventricle, *Am. J. Physiol.* 120: 635, 1937.
35. Katz, L. N.: The Asynchronism of Right and Left Ventricular Contractions and the Independent Variations in Their Duration, *Am. J. Physiol.* 72: 655, 1925.
36. Jochim, K., Katz, L. N., and Mayne, W.: The Monophasic Electrogram Obtained From the Mammalian Heart, *Am. J. Physiol.* 111: 177, 1935.
37. Eyster, J. A. E., Maresh, F., and Krasno, M. R.: The Nature of the Electrical Field Around the Heart, *Am. J. Physiol.* 106: 574, 1933.
38. Eyster, J. A. E., Maresh, F., and Krasno, M. R.: The Nature of the R Wave Potentials in the Tortoise and Frog Heart, *Am. J. Physiol.* 110: 422, 1934.
39. Krasno, M. R., Eyster, J. A. E., and Maresh, C. A.: Nature of T Wave Potentials in Tortoise Heart, *Am. J. Physiol.* 114: 119, 1935.
40. Schellong, F., Schwingel, E., and Hermann, G.: Die praktisch-klinische Methode der Vektordiagraphie und das normale Vektordiagramm, *Arch. f. Kreislaufforschung* 2: 1, 1937.
41. Wilson, F. N., Macleod, A. G., and Barker, P. S.: The Order of Ventricular Excitation in Human Bundle-Branch Block, *AM. HEART J.* 7: 305, 1932.
42. Brown, W. H.: A Study of the Esophageal Lead in Clinical Electrocardiography, *AM. HEART J.* 12: 307, 1936.
43. Katz, L. N., and Korey, H.: The Manner in Which the Electric Currents Generated by the Heart Are Conducted Away, *Am. J. Physiol.* 111: 83, 1935.
44. Robinow, M., Katz, L. N., and Bohning, A.: The Appearance of the T Wave in Lead IV in Normal Children and in Children With Rheumatic Heart Disease, *AM. HEART J.* 12: 88, 1936.

THE EFFECT OF FEVER ON POSTURAL CHANGES IN BLOOD PRESSURE AND PULSE RATE*

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IN THE course of artificial fever therapy it has been observed that a change in the position of the patient from the recumbent to the sitting position resulted occasionally in marked weakness, fainting, and even unconsciousness and convulsions. It is a reasonable a priori assumption that this is due to a rapid and marked drop in the blood pressure caused by extensive vasodilation and faulty adjustment of the vasopressor mechanism to changes in body posture.

Ellis and Haynes¹ have reported that postural hypotension is more likely to occur in patients who have some disease of the central nervous system. As most of the patients receiving fever therapy in our clinic have neurologic disease, and as fever therapy causes considerable stress and strain on the cardiovascular system, it seems likely that the ability of the vasopressor system to adjust itself during and immediately following fever would be lessened. A study was therefore undertaken to determine the effect of postural change on the pulse rate and the systolic and diastolic blood pressures in the basal state, at the height of fever, and again as the temperature fell toward the normal level.

MATERIAL

Observations were made on forty patients, twenty-nine males and eleven females, whose ages varied from 17 to 52 years, with an average age of 39½ years. The patients received fever therapy for the following conditions:

1. Twenty-two patients—*general paresis*. In this group are included one patient with syphilitic aortic regurgitation, two patients with syphilitic aortitis, and one patient with a "funnel chest" and displacement of the heart to the left anterior axillary line.

2. Six patients—*meningovascular neurosyphilis*. In this group is included one patient with syphilitic aortitis.

3. Four patients—*tabes dorsalis*.

4. Six patients—*multiple sclerosis*.

5. One patient—*congenital syphilis and interstitial keratitis*.

6. One patient—*rheumatic heart disease and subacute arthritis* of undetermined etiology.

METHODS

With but few exceptions, all observations were made under fasting conditions. Following a rest period of from 30 to 45 minutes in the recumbent position, repeated blood pressure and pulse rate determinations were obtained during a period

*From the Boston Psychopathic Hospital, under the direction of Dr. Harry C. Solomon, Chief of Therapeutic Research.

Received for publication Nov. 17, 1938.

of 10 to 20 minutes before and after fever therapy, and over a shorter period of time when the temperature was at its maximum. After these observations were obtained in the recumbent position in each of the three phases, the patient was sat up, and readings were again obtained at intervals of 5, 30, 60, 120, and 180 seconds. The patient was then placed back in the recumbent position and readings obtained each minute thereafter for five consecutive minutes. These procedures were carried out when the body temperature was normal, following the administration of two to five hours of artificial fever at temperature levels ranging from 103° to 106.5° , and when the body temperature had fallen to, or close to, the basal level.

Fever was induced by means of diathermy or inductothermy combined with the lamp cabinet, the lamp cabinet alone, and the Kettering hypertherm.

RESULTS

Pulse Rate.—The pulse rate rose in all patients when the sitting position was assumed, both before and after the induction of fever, with the exception of two patients in whom a fall occurred at the height of the fever. The increase in pulse rate and the percentage change with the shift in posture were greatest when fever treatment was completed and body temperature had fallen to nearly basal levels (Fig. 1).

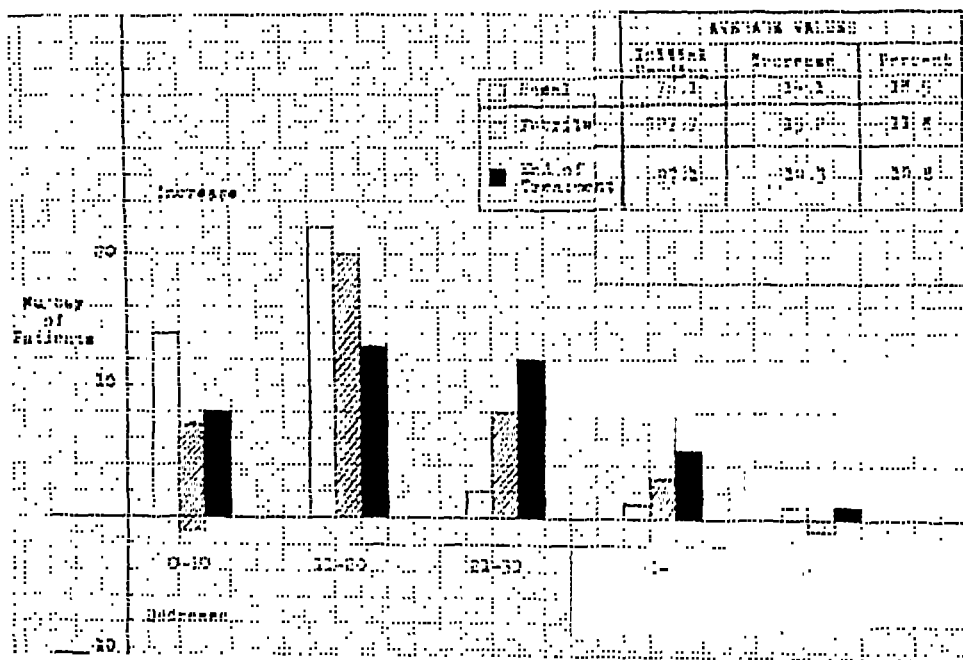


Fig. 1.—The effect of postural change on the pulse rate.

Systolic Blood Pressure.—As a result of the application of fever, the systolic blood pressure was likely to show an immediate and greater fall within 30 seconds after the change to the sitting position (Tables I and II). A compensatory rise in systolic pressure occurred less frequently under these conditions than before fever was induced. Whereas the systolic blood pressure showed a fall in only three patients when the sitting position was assumed under basal conditions, this occurred

TABLE I

EFFECT OF CHANGE OF POSTURE ON THE SYSTOLIC BLOOD PRESSURE UNDER BASAL CONDITIONS, DURING HYPERTYXIA, AND AFTER THE TERMINATION OF FEVER TREATMENT

AVERAGE PRESSURE BEFORE TEST	RISE ONLY				RISE AND FALL				FALL ONLY			
	NO. PATIENTS	RANGE IN MM.	AVERAGE VALUES MAX.	AVERAGE VALUES MIN.	NO. PATIENTS	RANGE IN MM.	AVERAGE VALUES MAX.	AVERAGE VALUES MIN.	NO. PATIENTS	RANGE IN MM.	AVERAGE VALUES MAX.	AVERAGE VALUES MIN.
Basal 107.7 mm.	28	0-30	18.9	9.6	9	+20 to -14	+8.0	-7.0	3	- 2 to -18	-12.0	- 3.0
Febrile 100.5 mm.†	6	3-27	17.1	8.3	11	+16 to -13	+6.9	-6.4	23	0 [‡] to -53	-19.7	-11.0
End of Treatment 93.3 mm.	16	1-31	16.8	6.0	16	+17 to -21	+6.4	-8.3	7	- 1 to -42	-18.5	- 8.7

*Decrease of 180-195 mm. omitted.

†Reading of 300 mm. omitted in average.

TABLE II

MINIMUM SYSTOLIC PRESSURE LEVELS BEFORE AND AFTER THE CHANGE IN POSTURE*

	SYSTOLIC BLOOD PRESSURE		
	50-60 MM.	61-70 MM.	71-80 MM.
Before Treatment			
Recumbent	0	0	3
Sitting	0	0	1
At Height of Fever			
Recumbent	0	1	6
Sitting	4	2	9
End of Treatment			
Recumbent	0	2	4
Sitting	3	4	7

*The incidence of low systolic pressures is greater when the sitting position is assumed during and after the application of artificial fever.

in twenty-three patients at the height of the fever and in seven patients after body temperature had fallen. (It should be pointed out that the application of fever results in a lowering of the average systolic blood pressure.)

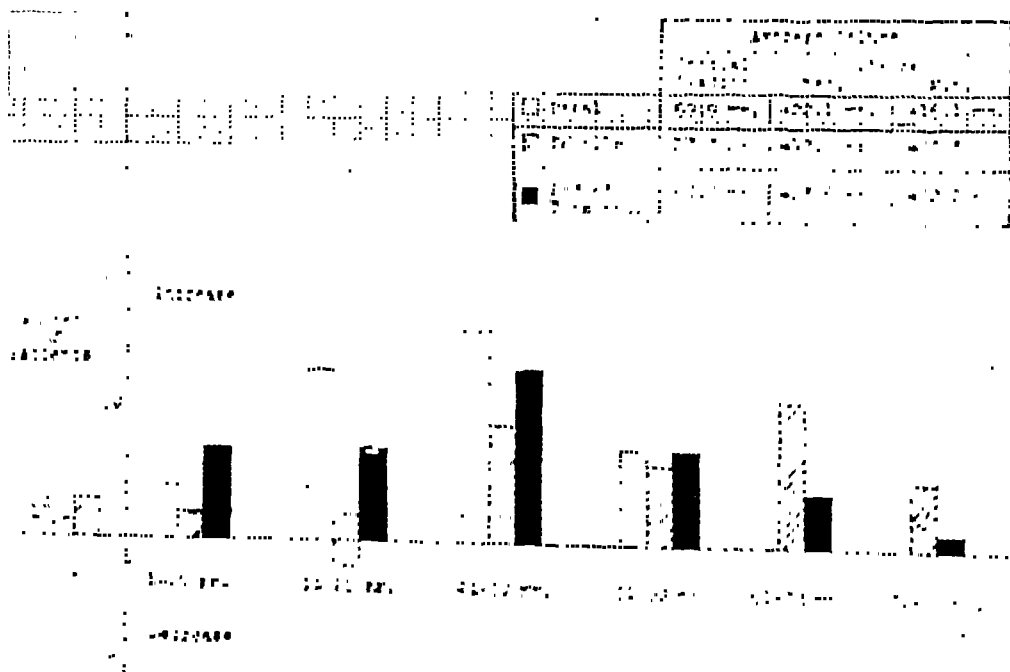


Fig. 2.—The effect of postural change on the diastolic pressure.

Diastolic Pressure.—In the basal state the change in position caused a rise in the diastolic pressure in all of the patients (Fig. 2). Both at the height of the fever and after the temperature had approached normal, the rise in diastolic pressure was greater and in some instances was quite marked. This was offset somewhat by the low diastolic pressure due to fever per se.

From these findings it becomes evident that in some patients during the febrile state, or immediately after the temperature has fallen, a change from the recumbent to the sitting position causes, as the most significant finding, a marked reduction in the pulse pressure due to a relatively small rise, no change, and, very often, a fall, in the systolic pressure, and a considerable rise in the diastolic pressure (Table III).

On resuming the supine position, from the sitting posture, the return of the blood pressure and pulse rate to the initial levels present before the test was applied was fairly prompt, occurring within two minutes in most patients under basal conditions, but taking more time after body temperature had fallen, and still more at the height of fever.

TABLE III

MINIMUM PULSE PRESSURE LEVELS BEFORE AND AFTER THE POSTURAL CHANGE*

	PULSE PRESSURE	
	6-9 MM.	10-15 MM.
Basal		
Recumbent	0	0
Sitting	0	3
Febrile		
Recumbent	0	0
Sitting	1	13
End of treatment		
Recumbent	0	0
Sitting	3	8

*Marked reductions in the pulse pressure are more frequent when the sitting position is assumed during and after the application of artificial fever.

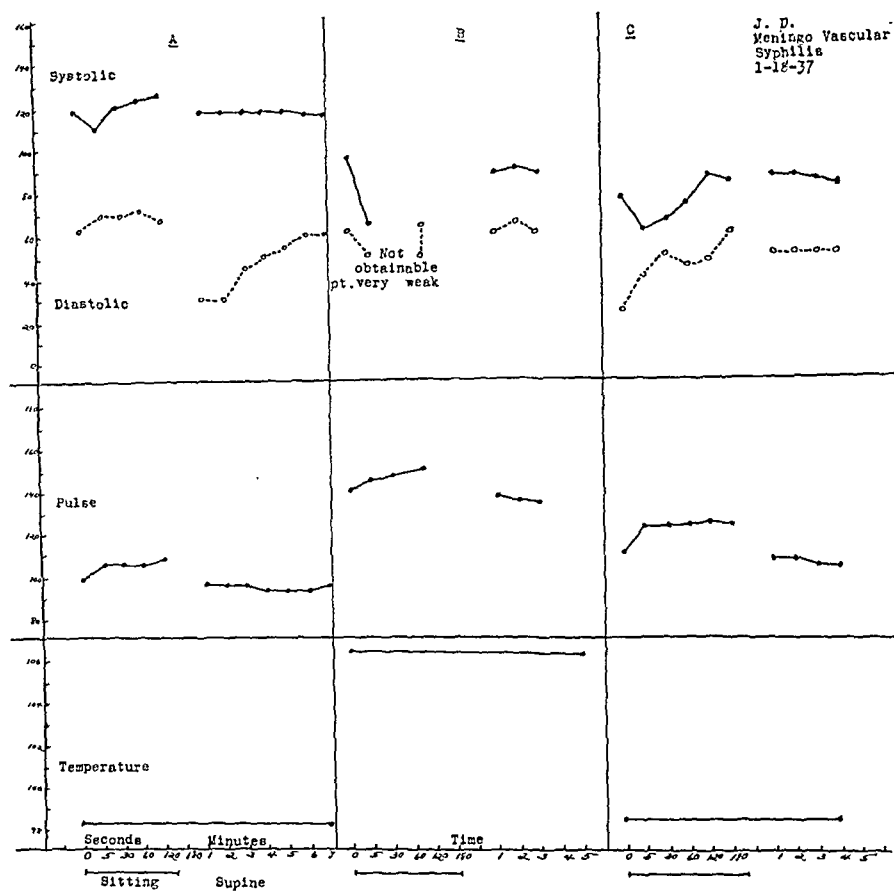
A division of the patients into two groups, those whose basal systolic blood pressures were above 120 mm. and below 100 mm. respectively, reveals that the initial systolic level was of little significance in the type of response obtained either at the height of the fever or after body temperature has fallen. A division of the patients with paresis into those having severe, intermediate, and mild degrees of the disease results in a similar conclusion. Though only four patients with tabes dorsalis are included in our series, it is our impression that adjustment to postural change was more difficult in these patients than in those with general paresis. As a group, the responses of the patients with multiple sclerosis to postural changes under the various conditions were good.

The increases in pulse rate in the individual patient with the change in posture were variable, tending to be greater at the height of the fever and greatest at the end of treatment. However, individual differences were present, the increases in some being about equal on each test or even less while body temperature was increased. In one male patient, 44 years of age, who was thought to have general paresis, a rather marked fall in pulse rate, from 136 to 87 beats, occurred with assumption of the sitting position when the rectal temperature was 106.2° F. The pulse rate rose to 126 while the sitting position was maintained for two and a half minutes, but did not reach the level present before the change in posture.

The changes in the systolic blood pressure in the individual patient were somewhat variable. However, those patients who exhibited both a rise and a fall, or a

fall alone, in the systolic pressure under basal conditions usually responded in a similar fashion, or showed a fall alone, at the height of the fever and at the end of treatment. It is evident also that other patients who responded with an increase in the systolic pressure under basal conditions showed a different response during and after fever, either fluctuations in both directions or reductions alone.

In two patients, J. D. (52 years old, meningovascular neurosyphilis), and C. A. (56 years old, tabes dorsalis), the change to the sitting position at the height of the fever was accompanied by changes in the blood pressure and the pulse rate characteristic of postural hypotension (Figs. 3 and 4).



Figs. 3 and 4.—The alterations in the blood pressure and pulse rate produced by changing to the sitting position at the height of the fever resemble those seen in postural hypotension. A, Before fever induction; B, at height of fever; C, at end of treatment.

In one patient (36 years old, multiple sclerosis), the initial systolic pressure in the supine position at a temperature of 104° F. before the test was carried out was 300 mm. on numerous occasions. The change to the sitting position resulted in a drop to 105 mm. The marked increase in the systolic pressure at the height of fever, at a time when there is usually a slight fall or rise in most patients, seems incredible, but the measurements obtained on five consecutive minute readings following the resumption of the recumbent position ranged from 210 mm. to 100 mm. (Observations on the blood pressure of a large group of patients given artificial fever by similar methods have revealed in a number of patients blood pressure values ranging from 240 mm. to 300 mm. over periods of one to two hours.)

DISCUSSION

Compensation is usually prompt and adequate with a change in body position. A change from the recumbent to the standing position in the normal person is accompanied by only slight fluctuations in the systolic pressure, usually less than 10 mm. in either direction, slight increases in the diastolic pressure, and only slight decreases in the pulse pressure. The heart rate may increase from 10 to 20 beats a minute.¹ These

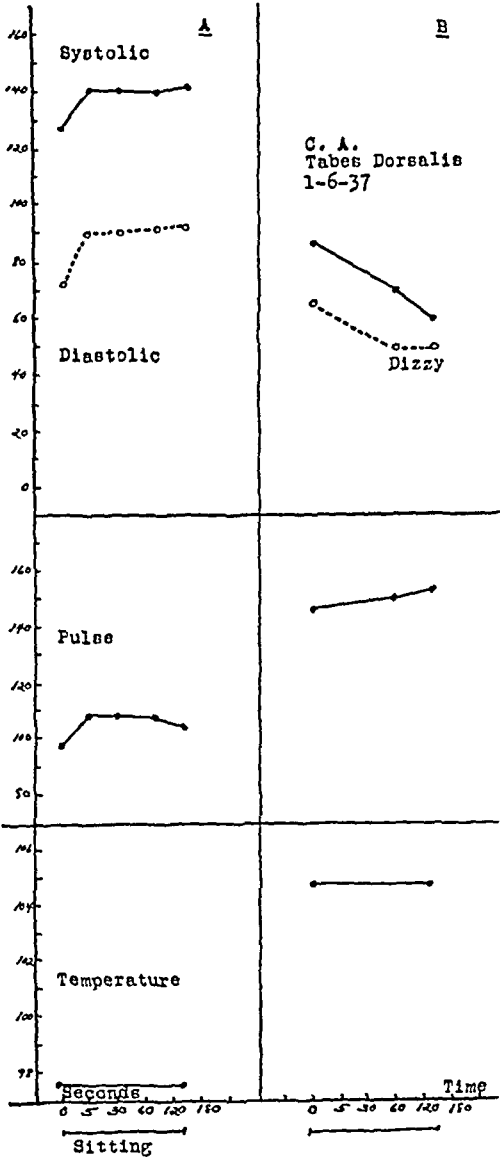


Fig. 4.

changes tend to overcome any pooling of blood in the areas below the level of the heart and to maintain an adequate blood supply to the brain. A diminution of the latter stimulates the vasomotor center, which sends out impulses constricting the arterioles. Of considerable importance in the adjustment to postural change is the vasoconstrictor action in the splanchnic area, which in man prevents a fall in blood pressure.²

Various types of inadequate responses to postural change occur. Adaptation may be insufficient immediately on the assumption of the upright position with subsequent full compensation, or compensation may be good but as the position is maintained adaptation becomes inadequate. In the latter case the systolic pressure falls steadily, the diastolic pressure remains the same or may increase slowly, and the heart rate continues to rise. The postural reflex may be delayed, as shown by an initial fall in the blood pressure, or it may respond with insufficient intensity. It may respond excessively, as shown by a rapid heart rate or by the maintenance or increase in the diastolic blood pressure.¹

Changes in the systolic and diastolic blood pressures and pulse rate should be less pronounced when changing from the supine to the sitting position than from the supine to the standing position. Under basal conditions, the changes which occurred in our patients when the sitting position was assumed were often less marked than those found by others in patients changing to the erect posture. In some, however, the increases in pulse rate, systolic pressure, and especially the diastolic pressure, were much greater. The more marked increases in the pulse rate have been attributed to greater efforts on the part of the heart to maintain circulatory equilibrium.³ In addition, individual variations in the responses of the pulse rate and blood pressure to postural change are considerable.⁴

From the results obtained in our patients it is evident that the ability to adapt to postural change is made more difficult by the induction of artificial fever, and that this difficulty persists even after body temperature has fallen to, or close to, its basal level.

Difficulties in adjusting to the change from the recumbent to the sitting position under these conditions are revealed by:

1. The greater incidence of an immediate or a sustained fall of the systolic blood pressure to low levels.
2. More frequent fluctuations in blood pressure above and below the initial level present in the supine position.
3. Inability to maintain an initial rise in systolic pressure.
4. A fall of diastolic pressure, or inability of the diastolic pressure to rise.
5. Greatly reduced pulse pressure.
6. Greater and progressive increases in the pulse rate.

Observers have attributed inadequate adaptation to postural changes to impairment of intrinsic vascular tone or poor tone in the skeletal musculature, especially of the abdomen and legs, resulting in pooling of the blood in the dependent areas (either because of poor venous tone or failure of the skeletal muscles to assist in venous return), insufficient

cardiac output, and cerebral anemia.¹ Difficulty in postural adaptation has been observed in patients convalescing from severe infections, debilitated patients, and in patients with vasomotor instability and the effort syndrome.¹

Body musculature is considerably relaxed during and following artificial fever therapy and dehydration of a variable degree also frequently occurs,⁵ both resulting in an inadequate venous return and a diminished cardiac output. The change from the supine to the sitting position reduces still further the cardiac output⁶ and cerebral blood flow.⁷

Marked peripheral vasodilation is present as a result of artificially induced fever and, if long continued, capillary tone is impaired, with consequent stasis.⁸ Visceral engorgement is marked and is intensified by gravity when the sitting position is assumed, diminishing still further the venous return. The long continued application of artificial fever may result in exhaustion of the sympathetic nervous system,⁹ and since the responses of the vasomotor reflexes to postural change are mediated through the sympathetic nervous system,¹ they may become inadequate.

The prompt rise of the diastolic blood pressure in most of the patients when the sitting position was assumed during and following fever would seem to indicate that vascular tone was but slightly impaired as a result of fever. However, the inability of the systolic pressure to rise with the change in posture might well be due either to impaired vascular tone or to a diminished output for each heart beat.

The weakness, fainting, and convulsions which occurred in some of the patients as a result of the change to the sitting position, both at the height of fever and after body temperature had fallen, can be attributed, therefore, to diminution of the cerebral blood flow, not only as a result of the change in posture per se, but also because of the insufficient venous return due to dehydration, visceral engorgement, and possibly an impaired vasopressor mechanism. This is substantiated by the fact that when the sitting position was assumed at these times there were more frequently a fall in systolic blood pressure to low levels and a relatively large reduction in pulse pressure.

Similar alterations in response to changes in posture are said to occur as a result of anesthesia. Under chloroform, and to a less extent under ether and other anesthetics, also during shock and various unconscious states, the compensatory responses to changes from the horizontal position are depressed, and any change from this position may result in serious danger to life.¹⁰ It has been shown that general anesthesia, narcotic drugs, injections of histamine or barbiturates, severe anoxemia, and pulmonary hyperventilation will often depress considerably, or even abolish, the pressoreceptive regulation of the blood pressure and the circulation.¹¹ It has also been shown that the administration of vasodilator drugs, such as histamine and sodium nitrite, destroys the normal

compensatory reactions of the vasomotor system when there is a change from the horizontal to the upright position.¹² It is quite possible that artificial fever, as induced under the above conditions, may have a similar effect.

The fact that no symptoms and no abnormal responses were noted in some patients did not eliminate the possibility of an abnormal response when the patient was allowed to walk or stand. Patient D., though she responded in what appeared to be a normal manner to the tests applied, experienced a series of convulsive seizures when allowed to walk to the balance for a weight determination at the end of treatment. Patient C. A. had a convulsion when he attempted to stand following his treatment. Though muscular movements result in a greater venous return, the demands made upon the vasopressor and cardiovascular mechanisms when standing or walking following fever therapy are much greater than when changing from the supine to the sitting position, and inadequate responses, with symptoms, are more apt to occur.

The responses in blood pressure and pulse rate occurring in some of the patients at the end of treatment, when body temperature was nearly normal, were even more abnormal than those obtained at the height of the fever, indicating that residuals of the stress upon the cardiovascular and nervous systems are still present even when treatment has been completed.

The presence of heart disease due to syphilis or rheumatic fever in five of our patients did not appear to influence the results obtained in these patients, since the responses did not differ in any way from those which occurred in the patients without cardiac disease. There were, however, no signs of myocardial insufficiency in these five patients.

Our findings appear also to corroborate the statements of other workers^{1, 7} that dizziness and fainting are most likely to occur with postural change when other factors promoting cerebral anemia, such as arteriosclerosis, are present, for in our series symptoms were most prominent in patients above 50 years of age. However, an initially low blood pressure did not play as important a role and did not appear to bear any relationship to difficulties in adaptation, either before, during, or after the application of fever. Untoward symptoms did not result in all patients whose systolic blood pressure had fallen to low levels in the sitting position, indicating that there was no absolute level at which difficulties would occur.

It was interesting that some of the patients, when placed in the sitting position during fever and after body temperature had fallen, had excessive sweating over the face and shoulders, accompanied by pallor and very little sweating over the remainder of the body. In others the change in posture under these conditions was followed by dyspnea, eructations of gas, restlessness, nausea, weakness, dizziness, or blurring of vision.

SUMMARY

1. Studies were carried out to determine the effect of artificial fever upon the responses of the blood pressure and pulse rate to changes in body posture.

2. The application of artificial fever results in a greater frequency of inadequate responses to postural change, more marked at the height of the fever than when body temperature has fallen.

3. Inability of the postural vasomotor reflex to respond in a normal manner under these conditions is revealed especially by the more frequent immediate and sustained drop in the systolic blood pressure, and by rather marked reductions in pulse pressure.

4. Untoward reactions, such as fainting, unconsciousness, and convulsions, brought on by changes in body posture during or after the induction of artificial fever, are due to cerebral anemia caused by a diminished cardiac output and an impaired vasopressor mechanism.

REFERENCES

1. Ellis, L. B., and Haynes, F. W.: Postural Hypotension With Particular Reference to Its Occurrence in Disease of the Central Nervous System, *Arch. Int. Med.* 58: 773, 1936.
2. Roth, G. M.: The Postural Effects on Blood Pressure Following Interruption of the Vasomotor Nerves of Man, *AM. HEART J.* 14: 87, 1937.
3. Mortensen, M. A.: Blood Pressure Reactions to Passive Postural Changes. An Index to Myocardial Efficiency, *Am. J. Med. Sc.* 165: 667, 1923.
4. Ghrist, D. G.: Variations in Pulse and Blood Pressure With Interrupted Change of Posture, *Ann. Int. Med.* 4: 945, 1931.
5. Gibson, J. G. 2nd, and Kopp, I.: Studies in the Physiology of Artificial Fever I. Changes in the Blood Volume and Water Balance, *J. Clin. Investigation* 17: 219, 1938.
6. McMichael, John: Postural Changes in Cardiac Output and Respiration in Man, *Quart. J. Exper. Physiol.* 27: 55, 1937.
7. Loman, J., and Myerson, A.: Studies in the Dynamics of the Human Cranio-Vertebral Cavity, *Am. J. Psychiat.* 92: 791, 1936.
8. Krogh, A.: The Anatomy and Physiology of Capillaries, New Haven, 1924, Yale University Press, pp. 232 & 235.
9. Kopp, I., and Solomon, H. C.: Shock Syndrome in Therapeutic Hyperpyrexia, *Arch. Int. Med.* 60: 597, 1937.
10. Best, C. H., and Taylor, N. B.: Physiological Basis of Medical Practice, Baltimore, 1937, William Wood and Company, p. 220.
11. Heymans, C.: The Pressoreceptive Mechanisms for the Regulation of Heart Rate, Vasomotor Tone, Blood Pressure and Blood Supply, *New England J. Med.* 219: 147, 1938.
12. Loman, J., Dameshek, W., Myerson, A., and Goldman, D.: Effect of Alterations in Posture on the Intra-Arterial Blood Pressure in Man. II. Pressure in the Carotid Artery in Arterio-Sclerosis, During Syncope and After the Use of Vasodilator Drugs, *Arch. Neurol. & Psychiat.* 35: 1225, 1936.

EMBOLISM AND THROMBOSIS OF THE ABDOMINAL AORTA

REPORT OF THREE UNUSUAL CASES

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THERE have appeared in the recent medical literature reports of approximately 135 cases of embolism and thrombosis of the abdominal aorta, of which 125 were ably abstracted by Rothstein,¹ in 1935. Of the 135 patients, only twenty survived, ten by virtue of the development of an adequate collateral circulation, as reported by Gull and Chvostek,^{2a} Nunez,^{2b} Derman and Dutkewitsch,³ van der Beek,⁴ Bull,⁵ and Rykert and Graham.⁶ One recovered spontaneously and two improved under treatment with alternating suction and pressure. In one case reported by Rothstein the patient recovered, probably because the embolus passed from the bifurcation of the aorta into the iliac artery. The remaining nine patients were relieved by embolectomy. Death was usually not long delayed, following close upon gangrene of one or both legs. In Hesse's⁷ series of forty-six cases, the duration of life after the onset of embolic symptoms was as follows: nine patients died within twenty-four hours, six more within forty-eight hours, a total of twenty-four within one week, a total of thirty-five in the first month, and the remaining eleven patients all died between the second and sixth month. In the three cases presented in this article death occurred from twelve months to five years after the initial embolic symptoms. In two of the three there was no evidence of gangrene, and the immediate cause of death was intercurrent disease.

In contradistinction to embolism of the abdominal aorta, which is characterized by dramatic, sudden onset, as illustrated by Welch,⁸ primary thrombosis of this artery may be ushered in by slight, easily mistaken, or overlooked symptoms. In the majority of cases there is a primary embolus, followed by retrograde thrombosis of the involved artery. In these latter cases the classical sign of gangrene of an extremity may be late or entirely absent, depending on the speed of extension of the occluding thrombus up the vessel. Bull,⁵ however, states that the presence or absence of gangrene depends upon whether the lumen is completely or partially occluded.

To illustrate a marked degree of occlusion of the aorta with a minimum of symptoms of arterial obstruction, three cases of complete thrombosis of the abdominal aorta are presented in some detail.

REPORT OF CASES

CASE 1.—W. O., a 21-year-old grocer's clerk, was admitted to the North Country Communities Hospital, Glen Cove, L. I., on three occasions over a three-year period.

Received for publication Nov. 18, 1938.

He was first admitted April 2, 1933, with the history that two weeks prior to admission he had been forced to cease work because of tightness of the muscles of the left arm and of the calves of his legs. This condition was aggravated by exertion and relieved by sitting or lying down. Aside from the pain, the patient had noted no abnormality in either arms or legs. Two days before admission he was awakened in the night with a severe pain in his upper abdomen which was associated with nausea and vomiting. The pain and vomiting persisted the following day, and he was hospitalized for this complaint.

The family, past, and personal histories were entirely negative. The patient was a moderate user of tobacco.

The examination on admission revealed that the patient was a fairly well-nourished white man, not cyanotic or dyspneic. The blood pressure in the right arm was 130/78; in the left arm it could not be measured. No pulse was perceptible in the left arm. Whether or not there were pulsations in the femoral arteries was not ascertained. The heart sounds were normal. The abdomen was *scaphoid and showed no localized tenderness or rigidity*. Bilateral costo-vertebral tenderness was present, more pronounced on the right side than on the left. The extremities were normal.

Laboratory Examination.—The urine was normal. The hemoglobin was 88 per cent, the erythrocyte count 4,550,000, and the leucocyte count 9,500; 75 per cent of the leucocytes were polymorphonuclear cells. The blood Wassermann reaction was negative.

A roentgenologic examination of the chest failed to reveal any evidence of disease. Cholecystograms were reported as showing normal gall bladder function.

The patient remained in the hospital for eight days, during which time gradual improvement was noted. During the first three days of the hospital stay he continued to complain of vague abdominal pain. At no time were there any complaints referable to the legs, and no objective signs were found in the lower extremities.

The patient was next admitted to the hospital Jan. 24, 1934, approximately ten months after his first admission, with the history that his legs had become too weak to permit him to carry on his previous work as a grocer's clerk. He had also noticed that they became painful on walking. The pain and weakness had been noticed in lesser degree in the arms. He complained that his feet became cold more easily, and that epieritic sensation in the feet was diminished. "Ace" bandages applied to the legs had caused intolerable pain. About seven months before this second admission, the patient began having transient attacks of diplopia; this symptom had become more severe within the preceding week and had necessitated the second admission.

The examination on this admission revealed, in addition to the previous findings, that the heart was slightly enlarged to the left. A systolic thrill was felt at the apex. The pulmonic second sound was louder than the aortic second sound. There was a presystolic rumble at the apex. The blood pressure in the right arm was 140/80. No attempt was made to measure the blood pressure in the left arm. The neurologic examination revealed evidence of ataxia, as demonstrated by a positive Romberg test. A general weakness of the lower extremities was noted, and a slight involvement of the right seventh nerve and right third nerve nucleus, as evidenced by irregular pupils and ptosis of the left lid, was observed.

Laboratory examination again showed a normal urine and a normal blood count. A spinal puncture revealed that the spinal fluid was under normal pressure and contained the normal number of cells. While in the hospital the diplopia disappeared and the ataxia improved, so that the patient was discharged eleven days after admission with a tentative diagnosis of encephalitis.

The patient was next seen in the hospital twenty-three months later, Nov. 24, 1935. He said that for the preceding four days he had been short of breath. A cough which had been present for approximately one week had become worse and productive of bloody sputum, and was associated with pain in the anterior portion of the left chest. Hospitalization was advised when a marked pericardial friction rub was heard by his physician.

The interval history was otherwise negative except for the continued presence of intermittent claudication. There had been no diminution in cardiac reserve noted during the preceding two years.

The physical examination on this admission showed a dyspneic, pale, acutely ill, thin young man. Slight cyanosis and orthopnea were present. The pupils were slightly irregular but reacted normally to light and in accommodation. Evidence of marked hypertrophy of the left side of the heart was found; the lower outermost point of the apical impulse was in the sixth intercostal space, 14 cm. from the midsternal line. At the apex of the heart a marked pericardial friction rub was heard and gallop rhythm was present. There were a rough systolic and a high pitched diastolic murmur both at the apex and base of the heart. The blood pressure in the right arm was 190/100, and in the left arm 144/100. The blood pressure could not be measured in either leg. The lungs were dull to percussion, and there were moist râles at both bases. The liver was palpable below the costal border. It was not tender. Through the thin abdominal wall no pulsation of the abdominal aorta could be felt. It was noted that the femoral pulse on the right side was very weak, while no pulsation could be felt on the left. The extremities were otherwise normal.

The electrocardiogram showed sinus tachycardia, right axis deviation, and an auriculoventricular conduction time of .14 sec. The T wave was inverted in Leads I and II, and varied in Lead III. The precordial leads showed evidence of pericardial effusion, with depression of the ST segments in precordial Leads III and IV (method of Wilson, with the right arm lead wire connected to the exploring electrode).

Laboratory Examination.—On admission, the urine showed a very faint trace of albumin and three red blood cells to the high-power field. Red blood cells were not found on subsequent urine examinations, but granular casts appeared shortly before death. The hemoglobin was 62 per cent, the erythrocyte count 3,650,000, and the leucocyte count 9,000, of which 74 per cent were polymorphonuclear cells. The urea nitrogen content of the blood was 42 mg. per cent. The blood sugar and creatinine values were 150 and 2.2 mg. per cent, respectively. The blood culture on several occasions was sterile.

Röntgenologic examination of the chest at the time of admission showed a large pericardial effusion and soft, scattered pulmonary lesions suggesting lobular pneumonia. The findings were more marked in the central portion of the left lung.

The patient's condition grew steadily worse. The leucocytes gradually rose to 23,000, of which 84 per cent were polymorphonuclear cells. For the first few days the pericardial effusion was the predominant lesion. The friction rub remained for forty-eight hours. However, when fluids were forced the azotemia diminished, and within two weeks the pericardial effusion had disappeared. The gallop rhythm at the apex of the heart persisted. The veins of the neck remained distended throughout the entire hospital stay. Five days after admission the patient developed signs of fluid in the right side of the chest, and edema of the ankles which was more marked on the left side than on the right; the dyspnea and cyanosis increased, and the liver became palpable ten centimeters below the costal border. The patient was fully digitalized without effect. The orthopnea became more marked and the edema of the legs increased. The patient lapsed into semicomatose and expired sixteen days after admission. The total duration of the illness had been thirty-three months.

The pertinent autopsy findings were as follows: Upon opening the thoracic cavity 2,000 c.c. of bloody fluid were found in the right pleural sac, pressing the right lung to the mediastinum. Both lungs were riddled with infarcts of various sizes.

The lining of the pericardium was smooth and glistening throughout, with no areas of roughening or inflammation. Fifty cubic centimeters of pericardial fluid were present. The heart weighed 500 gm. The right auricle was normal. Enmeshed in the normal chordae of the tricuspid valve were found two large, extremely friable thrombi; the smaller one measured 1 cm., and the larger, 2 cm., in diameter. The right ventricle and pulmonary valve were normal. The aortic valve was bicuspid, and the cusps were found to be thickened, producing a hard, roughened, ragged, inelastic valve. At the tip of the larger (posterior) cusp there were very small, friable, well-organized vegetations. The wall of the left ventricle was markedly hypertrophied. The mitral valve and left auricle were normal.

The liver weighed 1,735 gm., and the cut section of this organ showed chronic passive congestion. The gall bladder was large and distended; the walls were normal. A large, gray, friable thrombus was noticed at the junction of the hepatic vein and inferior vena cava.

The spleen was small, shrunken, and of the fetal type.

The pancreas was normal.

The right kidney was large, of the fetal type, and weighed 217 gm.; this kidney was anomalous in that the main renal artery originated 2 cm. higher than the left renal artery. The left kidney was small, weighing 70 gm.; on section, the normal striations were lost, and the organ was of a darker hue than its fellow.

The arch of the aorta was normal. The intercostal arteries, especially over the lower half of the thorax, were slightly dilated. The thoracic aorta was not dilated, but showed more evidence of arteriosclerosis than is normal for a man 21 years old. Just below the diaphragm the aorta was occluded by an old, organized thrombus, covered with endothelium. Between the apex of the thrombus and its base, the right renal artery, which was entirely patent, was found. One centimeter below this artery was the celiac axis, which was completely occluded by thrombus. Below the celiac axis was the left renal artery, which was found to be partially occluded. Immediately below the left renal artery the aorta shrank to a diameter of 2 cm. Both of the common iliac arteries were thrombosed throughout their entire diameter (Fig. 1). The thrombus in the aorta and iliac vessels was identified as old and well organized. A collateral circulation had been established, in part, between the deep epigastric and internal pudendal arteries.

Microscopic examination of the aortic cusps showed that the bicuspid condition was of congenital rather than inflammatory origin, as demonstrated by Bishop,⁹ et al., with the Weigert elastic fiber stain, using the technique of Lewis and Grant.¹⁰

Microscopic study of the aorta revealed severe sclerotic changes of the intima and media, with laminated fibrinous thrombus filling the lumen. The lesions could not be identified by the pathologist as either syphilitic or rheumatic.

CASE 2.—V. T., a housewife, 42 years of age, was admitted to the Nassau Hospital, Mineola, L. I., in November, 1937, following a cerebral accident. The family history was negative. A history of rheumatic heart disease of two and a half years' standing was obtained. Eighteen months prior to admission she had had an infarct of the lung, with a slow recovery. Five months later an embolus had lodged in the left leg. This diagnosis was made because of coldness, pallor, and pain in the leg and foot, with inability to move the member. Within four months partial

function had returned. Residual weakness and intermittent claudication were the only remaining symptoms. There was no involvement of the bladder.

Physical examination of the patient on admission showed a dyspneic and orthopneic middle-aged woman. There was evidence of upper motor neurone paralysis of the left side. The heart was enlarged; the lower outermost point of the apical impulse was felt outside the midclavicular line. There were a systolic and diastolic murmur at the apex and a systolic murmur at the base. The ventricular rate was 100, the pulse rate 90. The blood pressure was 198/96. The spleen was not palpable. The liver was felt at the costal margin. The extremities were apparently normal. No discoloration was noted and the temperature of the legs was the same. There was no edema. Whether or not femoral artery pulsations were present was not ascertained.



Fig. 1.—Thrombosis of the abdominal aorta extending above the celiac axis (Case 1).

Laboratory Examinations.—The electrocardiogram showed auricular fibrillation. The urine was normal except for a faint trace of albumin and a few granular casts and leucocytes. The hemoglobin was 92 per cent and the erythrocyte count 5,360,000; the leucocytes numbered 20,400, of which 78 per cent were polymorphonuclear cells. The blood culture was sterile on two occasions. The blood Wassermann reaction was negative.

The patient remained in a state of semicoma and delirium, dying on the twenty-third hospital day with a rising ventricular rate and body temperature. The

paralysis remained unchanged. No circulatory changes were noted in the extremities throughout the entire period of hospitalization.

At autopsy there was a zone of softening, 6 cm. in diameter, in the right cerebral hemisphere, impinging on the lateral ventricle. The heart showed a right ventricle three times the normal thickness, a moderately thickened left ventricle, and an extremely stenotic mitral valve. On the posterior leaflet of the mitral valve there were numerous, red, calcific granulations. There was an adherent thrombus in the left auricle. The aorta in the upper portion was normal for the age of the patient. At the level immediately below the origin of the renal arteries the lumen of the aorta was occluded by a soft, red, but adherent, thrombus. This thrombus became firmer and more densely attached to the intima of the aorta as the bifurcation was approached. At this level the process was well organized. The contents of the lumen were yellowish gray and appeared partly fibrous. The process continued uninterrupted into the common iliac arteries.

The lungs showed diffuse congestion, but there was no evidence of pneumonia. The pleurae were covered by fibrous tissue; there was a small amount of fluid in both pleural spaces, from which the Type I pneumococcus was cultured. The spleen weighed 400 gm. and was grossly normal. The kidneys showed evidences of old infarction. The other organs were essentially normal.

Microscopic examination of the heart failed to show typical Aschoff bodies. There were, however, numerous foci of dense fibrous tissue around the blood vessels of the heart muscle.

Sections taken from that part of the aorta which was completely thrombosed showed the lumen with red thrombus adherent to the intima. Here the endothelium was deficient. The great part of the change lay in the media, where there were diffuse engorgement and reduplication of the small vessels and widespread infiltration of these tissues by polymorphonuclear cells and phagocytes containing hemosiderin.

The final diagnoses were rheumatic heart disease with mitral stenosis; mural thrombus of the left auricle; infarction of the right cerebrum; multiple old infarcts of the kidneys; acute fibrous and purulent pleuritis; diffuse mesoarteritis; and endoarteritis with thrombosis.

The autopsy findings were a surprise, for thrombosis of the aorta in this case was not suspected because of the paucity of symptoms referable to the abdomen and legs.

CASE 3.—H. B., a 54-year-old man whose mother had had hypertension, gave a past history which was essentially negative except for excessive cigarette smoking for many years.

The present illness began five years previously, when the patient noted a sudden pain in the left leg which was localized to the foot and calf and was associated with coldness of that member. This condition kept the patient in bed for three months, during which time there was improvement with the use of Buerger's exercises. Thereafter the patient's only symptoms had been intermittent claudication and partial loss of epicritic sensation of the left leg until three years prior to admission, when he had a similar attack with gangrene and loss of a small portion of the medial side of the left great toe. The toe later regenerated completely. He was subsequently treated by the Pavaex method, but noticed no lessening of the intermittent claudication. Fifteen months earlier he had had coronary occlusion, recovery from which was postponed by lobar pneumonia, the type and site of which were unknown to the patient. This occlusion was followed by a bilateral deep phlebitis of the legs and a subsequent pulmonary embolus. Still later there occurred an attack characterized by severe abdominal distention and hiccup which was diagnosed as mesenteric thrombosis. All these events took place over a ten-month period, during which the patient

was in a hospital in Canada practically the entire time. However, during the preceding four months he had been able to carry on his usual sedentary work as a writer, with no symptoms except intermittent claudication in both legs, worse on the left than on the right. There had been a loss of epicritic sensation in both feet. He had continued to smoke twenty to forty cigarettes a day until his admission to the Naussau Hospital. Two weeks prior to admission, following a great deal of walking, he noticed early gangrene of the third, fourth, and fifth toes of the left foot.

Examination on admission to the Nassau Hospital on March 22, 1938, showed a tall, spare, middle-aged man looking older than his years. The pupils were unequal, the right being larger than the left, but both reacted normally to light and in accommodation. Examination of the eye grounds showed moderate arteriosclerotic changes in the vessels. The cervical veins were not distended. The right lung was normal, but a few moist râles were heard at the base of the left lung. The heart was normal in size. The heart sounds were of fair quality at the apex and the base. There was a systolic murmur at the apex. The blood pressure in both arms was 136/80. The blood pressure could not be measured in either leg. The cardiac mechanism was normal, and the rate was 110 beats a minute. Neither the liver nor spleen was felt. The abdominal aorta was palpable through the thin abdominal wall down to the level of the umbilicus, where the pulsation abruptly ceased. There was marked sclerosis of the brachial and radial arteries. There was a very poor femoral pulsation on the right side, but a fair pulsation of the left femoral artery was felt. No dorsalis pedis or posterior tibial pulsation was noted in either leg. There was dry gangrene of the left third, fourth, and fifth toes, with regional cellulitis extending to the ankle. The temperature of the legs was the same. The veins were prominent, but no varicosities were present.

An electrocardiogram taken prior to admission showed changes typical of an old anterior wall infarction.

Laboratory Examination.—The specific gravity of the urine was 1.020; the urine contained no albumin or sugar. The blood Wassermann reaction was negative.

The patient's course in the hospital was characterized by slowly increasing dry gangrene of the entire left foot below the ankle, and by a sudden arterial occlusion in the right leg. This occlusion occurred seven days after admission, and resulted in a spreading dry gangrene of the right leg extending to mid-thigh. The patient was given the usual conservative treatment for gangrene, including alcohol by mouth, papaverine, tissue extract, generalized infrared light, and partially occlusive bandages to the leg. All treatment was to no avail. He became increasingly stuporous and "toxic" and had slight fever until the final week, when the temperature rose much higher. Death occurred suddenly eleven weeks after admission.

The pertinent autopsy findings were as follows: External examination showed dry gangrene of the left leg below the ankle and of the right leg below mid-thigh.

The lungs showed diffuse congestion. The heart weighed 375 gm. There was a definite increase in thickness of the wall of the left ventricle. Moderate generalized coronary sclerosis was present. The left descending coronary artery was found to be occluded and fibrosed by an old thrombus. At the apex of the left ventricle there was a large area of fibrosis, with an old, adherent, organized mural thrombus. There was no deformity of the valves. The heart was otherwise normal.

The arch and thoracic portion of the aorta were normal, showing only slight evidence of arteriosclerosis. There was no dilatation of the thoracic aorta and little increase in the diameter of the intercostal arteries. At the level of the

left renal artery the lumen of the aorta was completely obstructed by an organized thrombus, with a soft, fresh extension into the superior mesenteric artery. The right renal artery was patent, the left renal artery partially occluded. The thrombus continued into the common iliac arteries. The left iliac artery contained an old, white, organized thrombus, and the right iliac artery was obliterated by a more recent, red, fibrinous thrombus (Fig. 2). There was very little evidence of collateral circulation.

The upper pole of the left kidney was scarred by a large infarct which showed various stages of healing. The right kidney was normal.

The liver and spleen were grossly normal.

There was no evidence of gangrene or necrosis of the intestines.

Microscopic study of the thrombus at the level of the renal artery showed organization and no evidence of recanalization. The endothelial lining of the aorta was destroyed; the elastic layers were reduplicated, as demonstrated by the Weigert stain.

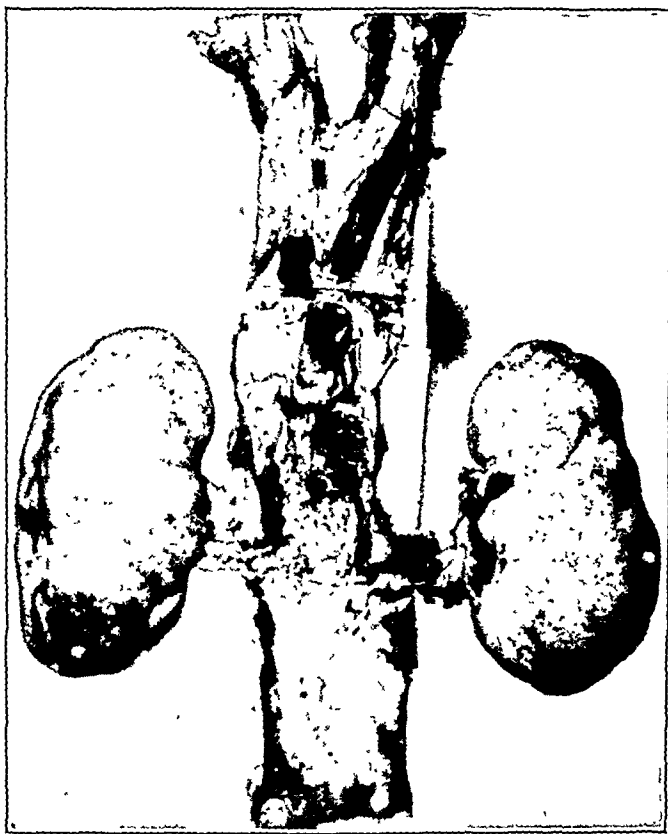


Fig. 2.—Two stages of thrombosis of abdominal aorta to the level of the renal arteries (Case 3).

COMMENT

It is interesting to compare the symptoms in these three cases with those in Rothstein's series of seventy-two cases (Table I). It is surprising, in view of the high extent of the thrombus in all three cases, and the organization present at the high level in two of these, that abdominal symptoms were not more marked and that spinal cord and bladder symptoms were not present in any case. The symptoms

in all three cases were caused by slowly decreasing blood supply. It is interesting to note that in two of the cases the abdominal aorta was found to be abnormal before death. This observation alone served to indicate the high extent of the lesions.

TABLE I

SYMPTOMATOLOGY OF OCCLUSION OF THE AORTA IN ROTHSTEIN'S¹ 72 CASES COMPARED WITH THAT IN THE 3 CASES HERE REPORTED

A. MANIFESTATIONS IN LOWER EXTERMITIES	PER CENT	CASES		
		1	2	3
1. Pain in legs	44.4	+	+	+
2. Loss of pulsation in arteries of lower extremities	40.3	+	?	+
3. Cyanosis or discoloration of lower extremities	22.2	0	0	+
4. Edema of lower extremities	6.9	+	0	0
5. Disturbances in sensation of lower extremities	40.3	+	+	+
6. Disturbances of muscle power of lower extremities	39.0	+	+	+
7. Preceding embolic phenomena in peripheral arteries of lower extremities	2.8	0	+	+
8. Intermittent limping	2.8	+	+	+
9. Disturbances in circulation beginning in one, and then in the other, extremity	16.6	+	+	+
10. Evidences of gangrene in lower extremities	57.0	0	0	+
a. Involving only the right lower extremity	12.5			
b. Involving only the left lower extremity	19.4			
c. One lower extremity (side not noted)	1.4			
d. Involving both lower extremities	23.7			+
B. MANIFESTATIONS OF INVOLVEMENT OF ABDOMINAL ORGANS	PER CENT	CASES		
		1	2	3
1. Pain in the abdomen	11.1	+	0	+
2. Pain in the back	5.5	+	0	+
3. Loss of pulsation of abdominal aorta	6.9	+	?	+
4. Incontinence of urine	6.9	0	0	0
5. Retention of urine	2.8	0	0	0
6. Incontinence of flatus	4.2	0	0	0
7. Hemorrhage from anus and urethra	8.3	0	0	0

Presence or absence of symptoms indicated by + or 0.

The fundamental lesions in all of these cases were different, but all led to the same terminal condition in the aorta and iliac arteries. As is noticed from the description in the microscopic reports, the endothelial wall of the aorta around the thrombus was destroyed in all cases. It is impossible to differentiate primary infection of the arterial wall from nonspecific reaction in cases of complete obstruction of long duration. In Case 1, the congenitally bicuspid aortic valve with roughening and organized small vegetations may have been a nidus for small emboli. No doubt the cerebral signs in this case were embolic. The symptomatology and course in this case were essentially that of progressive thrombosis superimposed upon small emboli. The long duration of life was possible only because of the anomalously high origin of the right renal

artery. In the second case, a mural thrombus in the fibrillating left auricle was the source of emboli, again with progressive superimposed thrombosis. In the third case the etiology was atherosclerosis, and the case was somewhat similar to one reported by Rosenberg,¹¹ et al. The use of the Weigert elastic stain was helpful in demonstrating the reduplication of the elastic fibers found in atherosclerosis.

CONCLUSION

Three cases of embolism and complete thrombosis of the abdominal aorta are reported; the fundamental lesions were etiologically different, but they all produced practically identical gross and microscopic changes in the aorta. The patients survived from one to five years after the onset of occlusive symptoms. Two of the three patients showed no evidence of gangrene in spite of the high level of the lesions.

These cases are reported to demonstrate, in addition to the unusual and widespread lesions, the ability of the circulatory system to adapt itself to a gradually occluding process, and to emphasize the fact that extensive pathologic changes may occur in the large vessels of the body with only minor symptoms.

REFERENCES

1. Rothstein, Jacob L.: Embolism and Thrombosis of the Abdominal Aorta in Infancy and in Childhood, *Am. J. Dis. Child.* 49: 1578, 1935.
- 2a. Gull and Chvostek: *Wiener Med. Blätter*, p. 1513, 1881.
- 2b. Nunez: *Gaz. Med. de la Habana* II, p. 160, 1879-80, quoted by Welch (reference 8).
3. Derman, G. L., and Dutkewitsch, E. A.: Zur Frage des vollständigen Verschlusses des unteren Teiles der Bauchaorta, *Virchow's Arch. f. path. Anat.* 274: 535, 1929-30.
4. van der Beek: Een geval van thrombose van de binkaorta, *Nederl. tijdschr. v. geneesk.* 76: 4538, 1932.
5. Bull, P.: Hvad kan over 6000 Obduktioner lare os om embolia resp. gangraena embolica extremitatum? *Norsk. mag. f. laegevidensk.* 83: 173, 1922.
6. Rykert, H., and Graham, D.: Some Problems in the Diagnosis, Prognosis and Treatment of Acute Arterial Occlusion, *AM. HEART J.* 15: 395, 1938.
7. Hesse, E.: Ueber die Embolie und Thrombose der Aorta abdominalis und ihre operative Behandlung, *Arch. f. klin. Chir.* 115: 812, 1921.
8. Welch, W.: Embolism and Thrombosis, In Albutt, I. C., and Rolleston, H. D.: *System of Medicine*, New York, vol. 6, p. 809, 1909, The Macmillan Company.
9. Bishop, Louis Faugeres, Bishop, Louis Faugeres, Jr., and Trubeck, Max: Aortic Stenosis of Inflammatory Origin With a Differential Study of the Acquired or Congenital Origin of a Bicuspid Aortic Valve, *Am. J. M. Sc.* 188: 506, 1934.
10. Lewis, T., and Grant, R. T.: *Heart* 10: 21, 1923.
11. Rosenberg, E. T., Keith, M. M., Wagener, H. P.: Diffuse Arterial Disease With Hypertension, *Arch. Int. Med.* 62: 461, 1938.

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DISSECTING ANEURYSM OF THE AORTA

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ALTHOUGH a mechanism by which dissecting aneurysm of the aorta may occur has been understood for more than 200 years,¹ the clinical diagnosis has, until recently, rarely been made. In 1856 the first account of a correct ante-mortem diagnosis was published by Swaine.² In an extensive review of the literature in 1933, Shennan³ accepted six ante-mortem diagnoses in 297 cases described. I have been able to find accounts of 24 additional cases⁴ in which the ante-mortem diagnosis was anatomically demonstrated to be correct. This figure does not include the case of Keinbock and Weiss,⁵ which seems convincing, but in which the diagnosis of the type of aneurysm rested solely on roentgenographic findings, nor does it include diagnoses unsupported by published details. The diagnosis has doubtless been correctly made in several instances which remain unreported.

This marked increase in the number of cases recognized has not been due to the development of any new diagnostic test or procedure, but is attributable solely to the increasing familiarity of alert practitioners with the clinical features of the condition. These features usually include a pre-existing hypertension. Syphilis is infrequently present. Most of the cases have occurred in males between forty and sixty years of age. The onset is usually sudden, often following some exertion or strain, with agonizing pain of a rending character, the location of which varies with the site of the aneurysm, but which characteristically exhibits a migratory tendency. It may begin anteriorly in the precordial region or in the epigastrium, pass to the neck or jaw, later to the back, the flanks, and the legs, or any of these areas may be involved. Radiation to the arms is less common than in myocardial infarction. The onset is also usually attended by pallor, perspiration, and prostration, and often by loss of consciousness. In some cases, however, pain is either absent or relatively insignificant. Once the aneurysm is formed, the symptoms are determined by the location and extent of the dissection. The typical features are well illustrated in the following three cases, in which the diagnosis was made during life; one of the patients survived for the remarkably long period of twenty-seven months.

CASE 1.—A clergyman, 45 years of age, first came under my observation on March 12, 1937, through the courtesy of Doctors A. M. Meads and Harold G. Trimble. At this time he was complaining of palpitation and shortness of breath of two weeks' duration. He had had, also, for some time, fatigue and a feeling of weight behind the sternum and in the left shoulder region, but no pain. Periodontal infection had been known to be present for a period of about two years.

Received for publication Dec. 8, 1938.

He was found to have auricular fibrillation, which was promptly abolished by means of quinidine. A faint systolic murmur could be heard at the apex, but there was no other evidence of heart disease. Peridental infection was demonstrated, and it was thought that this might have produced toxic myocarditis, and that the symptoms were aggravated by the emotional stresses resulting from the patient's temperament and type of life. The diseased teeth were removed, and the patient returned to work.

During April, there continued to be some complaint of a heavy feeling in the precordial region. The systolic apical murmur became more definite, and there were occasional premature beats. On May 21, some muffling of the aortic second sound was noted. The blood pressure was 100/75. Fluoroscopic examination showed some dilatation of the first portion of the aorta. The blood Wassermann reaction was reported negative. At this time there was some complaint of precordial distress at long intervals.

On July 25, 1937, the patient collapsed in his pulpit and was brought to the hospital. He stated that for several days previously he had had, at times, considerable discomfort behind the upper sternum, extending to the left shoulder region. He had not ceased his activities and, on the contrary, had visited a lake resort where he undertook considerable physical exertion. Immediately before the collapse he had a sensation of a couple of sharp "thuds" in his chest, followed by weakness.

On examination he was found to be in mild shock, with cold, clammy perspiration and coldness of the extremities. The pulse was rapid and of the Corrigan type. Loud aortic systolic and diastolic murmurs were present. The percussion outline was not appreciably changed. There was flaccid paralysis of the leg muscles, both anterior and posterior groups, on both sides, with weakness of the hamstrings. There was an area of anesthesia on the right side, beginning on the lateral aspect of the right thigh in the midportion, extending downward, encircling the leg at about the midportion, and involving the entire foot. The paralysis on the left side cleared up within a few minutes, but that on the right persisted.

On the following day a similar area of hypesthesia appeared on the left side, and also marked weakness of the muscles of the left leg and of the hamstrings. There was hypesthesia in the saddle area, and marked difficulty in voiding. The muscles of the right leg and foot remained paralyzed. A spinal puncture was done, and the fluid found to be entirely normal except for increased pressure. The muscles normal. There were a slight secondary anemia, low-grade fever, and leucocytosis. Supportive measures were employed, and large doses of iodides and customary doses of bismuth were given. The paresis and hypesthesia on the left side disappeared within a few days. The heart murmurs varied in quality and intensity from time to time. Fever and moderate leucocytosis continued, but the anemia did not increase. Repeated blood cultures, a second spinal fluid examination, and several blood Wassermann tests were entirely negative. A Kline exclusion test was also negative. Roentgenologic studies at the bedside were inconclusive. Electrocardiograms showed only slurring of the R wave of Lead III, and no evidence of coronary occlusion.

At this time we were having much trouble with the patient from the psychic standpoint. He had previously been observed to be a hypertonic, if not hypomanic, type, very intense, highly reactive, and emotionally unstable. His physical incapacity exaggerated these personality traits to the point of actual mental derangement. There were times when he would be intensely cyanotic, with respiration of a shallow, grunting character, and, occasionally, of Cheyne-Stokes type. These manifestations occurred mostly during sleep. A little later there was a rather intense, but transient, hematuria, without evidence of infection. The circulation in the legs gradually became more and more feeble, until the development of marked pain, with discoloration on the slightest pressure, made us fear gangrene. This was especially marked on

the right side. Death, which occurred September 4, 1937, was due to exhaustion and terminal bronchopneumonia.

Post-mortem examination, by Dr. Paul Michael, disclosed a rent through the intima, completely encircling the aorta, about an inch above the free margins of the aortic valve cusps. The valve was normal. The dissection had extended proximally, forming a large aneurysm, covered only by adventitia and visceral pericardium, which projected backwards and to the right within the pericardial sac, compressing the right auricle. Dissection had occurred distally around the aortic arch and posteriorly and slightly to the right, throughout the entire length of the descending

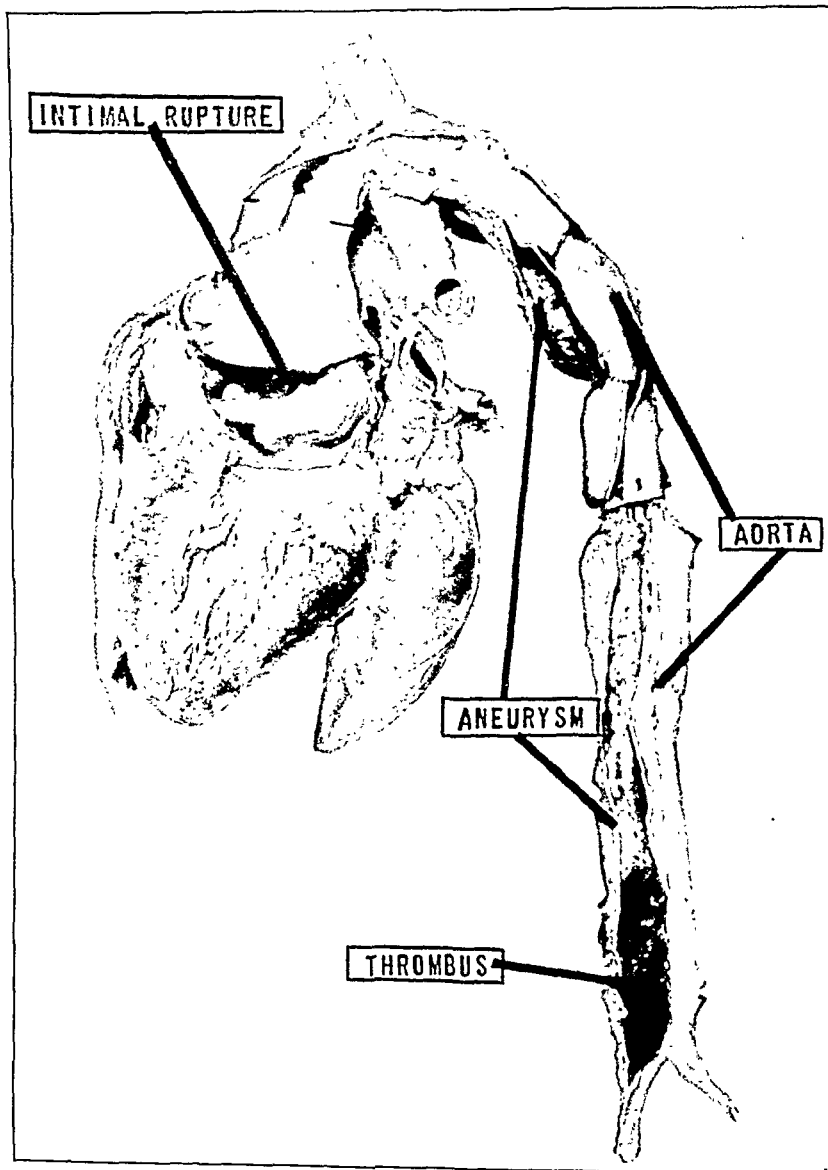


Fig. 1.—(Case 1) Anterior view, showing intimal rupture encircling the ascending aorta, with a dissecting aneurysm extending to the bifurcation. Note the large thrombus in the terminal portion of the aneurysm, mechanically obstructing the iliac orifices.

thoracic and abdominal portions of the aorta, stopping at the bifurcation. On the right side the intercostal arteries from the third to the eleventh, inclusive, were ruptured. The subcostal and lumbar arteries were ruptured bilaterally. The renal

arteries were considerably obstructed, especially the right. The terminal portion of the aneurysm was filled with thrombus and bulged into the lumen of the aorta at the bifurcation in such a way that the orifice of the right common iliac was almost completely obstructed and that of the left was markedly narrowed. The central nervous system was not examined.

Comment.—From the day of the July attack, dissecting aneurysm of the aorta seemed to me the most plausible diagnosis. As the symptoms progressed this impression became a positive conviction. The development of the heart lesions was too rapid for a syphilitic process, and the fact that the serologic reactions were persistently negative, even after iodide and bismuth treatment, was very much against such a diagnosis. To explain the neurologic changes as a result of sub-acute bacterial endocarditis would require the assumption that emboli had lodged in the lower lumbar and sacral segments of the cord, when

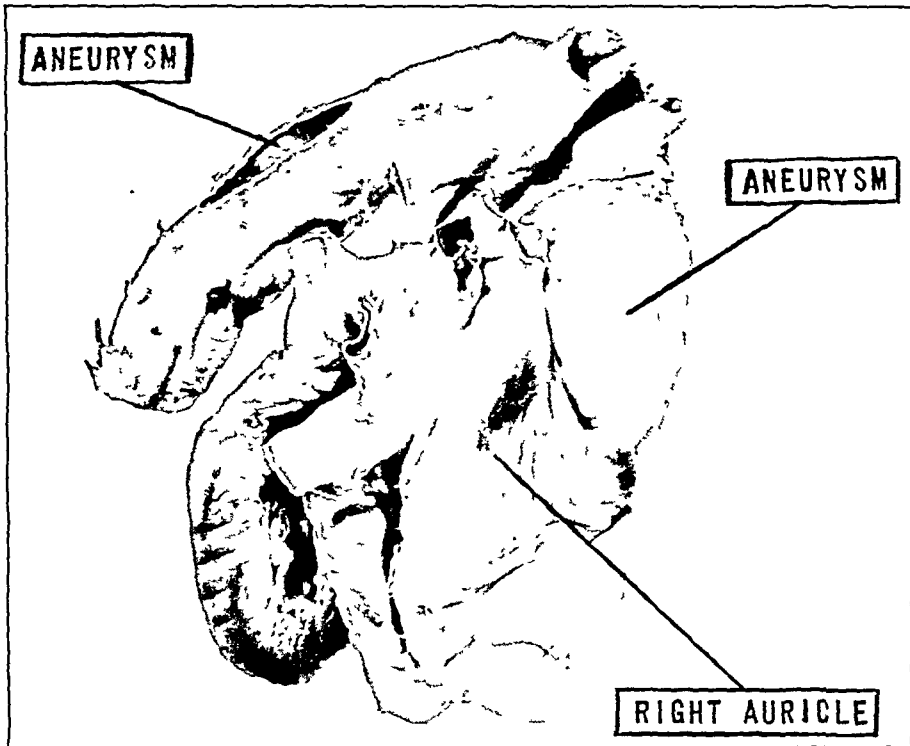


Fig. 2.—(Case 1) Posterior view. The parietal pericardium has been removed. Note the relation of the intrapericardial portion of the aneurysm to the right auricle.

there was no evidence of embolism elsewhere. This possibility seemed too remote for serious consideration. The persistently negative blood cultures and the failure of the anemia to progress were also against this diagnosis. On the other hand, the formation of a dissecting aneurysm could readily explain the sudden occurrence of collapse, with the rapid development of signs of aortic insufficiency from deformity of the aortic valve ring, and of neurologic signs from interference with the blood supply of the spinal cord. Extension of the aneurysm into one or

both renal arteries, or compression of these arteries by the aneurysm, could account for the hematuria. Compression of the iliac vessels could account for the circulatory impairment in the legs. Failure to demonstrate roentgenologic evidence of aneurysm did not militate against the diagnosis under the circumstances. Patients so acutely ill, in whom this diagnosis is being considered, often cannot be moved about with sufficient freedom to permit the utilization of all the refinements of radiographic technique required to visualize the structures involved.

This case illustrates the fact that the highly characteristic pain of dissecting aneurysm is not invariably present, even though the rent in the intima may be large and the aneurysm extensive. The case was also atypical in that there was no evidence of antecedent hypertension. The sudden collapse, with the coincident development of heart murmurs, fever, leucocytosis, anemia, neurologic manifestations, circulatory changes in the legs, and, finally, hematuria, led to the diagnosis. Although the occurrence of neurologic changes in the legs has been pointed out by others,⁶ their diagnostic significance has perhaps not been sufficiently emphasized, and an explanation of the mechanism of their production may be of interest. The upper portion of the spinal cord receives its blood supply from the subelavian arteries through the anterior and posterior spinal branches of the vertebral arteries. As the anterior and posterior spinal arteries course downward on the pia mater of the spinal cord, they are supplemented by anastomotic branches from the spinal branches of the vertebral arteries, the deep cervical arteries, and the intercostal and lumbar arteries. The first two pairs of intercostal arteries arise from the superior intercostal branches of the subelavian arteries, but the remaining intercostal arteries and the lumbar arteries arise directly from the posterior aspect of the aorta. Since dissecting aneurysms usually pass down the posterior wall of the aorta, rupture of several pairs of the intercostal and lumbar arteries not infrequently occurs. In this way there may be sufficient interference with the blood supply to the lower cord to produce impairment of sensory and motor function of variable extent and intensity. Because of the free anastomotic blood supply of the spinal cord, these changes will frequently be transitory. The occurrence of hematuria, or even anuria, as a result of extension of the aneurysm into the renal artery, has been previously described⁷ and is readily understandable. When the intima ruptures but a short distance above the aortic valve, dissection proximally is likely to deform the valve ring, giving rise to aortic insufficiency with its typical diastolic murmur and Corrigan pulse. Rupture of the aneurysm into the pericardial sac has frequently occurred at a point posteriorly and to the right, lateral to the right posterior cusp of the aortic valve. It was at this point that the large intrapericardial aneurysm formed in this case. It is likely that much of the dyspnea and cyanosis in this case was due to compression of the right auricle by this aneurysm.

The post-mortem examination unfortunately gave no clue to the nature of the lesions of the aorta which preceded the sudden collapse. That some such lesions existed is suggested by the complaint of precordial distress which preceded the attack by several months, and by the fluoroscopic finding of enlargement and increased density of the ascending portion of the aorta two months prior to the attack. The observations of Krukenberg⁸ and Tyson⁹ that the initial lesion in many of these cases is rupture of a vas vasorum and splitting of the walls of the aorta by the formation of a hematoma afford a possible explanation. The probability of the existence of such a mechanism is, however, purely a matter for speculation in the present instance.

CASE 2.—A retired postman, aged 68 years, was seen in consultation with Dr. A. Lyle Winslow, on Nov. 19, 1937. This man was known to have had hypertension for several years, and albumin and casts had been found in the urine. He had been as well as usual, however, until about two weeks previously, when, in the morning, after visiting the bathroom and starting to ascend the stairs, he was stricken with a severe agonizing pain which he said felt like knives turning and twisting about within his chest. The pain extended through to the back and into the epigastric region. It did not radiate to the arms. There was no dyspnea, although his breathing was somewhat restricted because of pain. He showed signs of shock, and large doses of morphine were required for relief of the pain. His blood pressure fell below 100, systolic, and there was some irregularity of the heart's action. Within the first day the pain subsided, but returned at intervals, though never so acutely. The blood pressure rose about to its previous level within a few days. Fever ranging to about 102° F. had been constantly present. An electrocardiogram, made three days following the attack, showed only left axis deviation, with none of the findings characteristic of coronary occlusion.

Examination revealed a large man, well-preserved for his stated age, sitting up in bed and moving about actively. He was of the hypertonic personality type, obviously willful and difficult to control. His lips and mucous membranes appeared a little cyanotic, but he was not dyspneic. The pulse rate was 104 and the pulse was regular, the blood pressure measured 160/100 in both arms, and the temperature was 101.6° F. The vessels of the extremities showed moderate sclerosis, but no beading. The pulsations were equal on both sides, somewhat diminished in the lower extremities but not out of proportion to the arteriosclerosis present. The head, neck, lungs, and abdomen were apparently normal. There was no peripheral edema. The heart did not seem appreciably enlarged to percussion, and the sounds were clear and distinct and of approximately normal quality. There was a faint, blowing, systolic murmur in the midprecordium, but no murmur could be heard along the spine. In the third week of the illness a second electrocardiogram was made which was not significantly different from the first. Fever and occasional mild retrosternal pain persisted until about six weeks after the onset, when death occurred suddenly.

Post-mortem examination showed a rent in the intima almost completely encircling the aorta in the descending portion of the arch. Dissection had occurred proximally about three centimeters and distally about eighteen centimeters. The terminal portion of the aneurysm was filled with organizing thrombus. The central portion had not thrombosed, and there was a large external rent through the adventitia and pleura into the left pleural cavity, which was filled with blood.

Comment.—Although the occurrence of pain of this character in a person of the kind described is highly suggestive of coronary occlusion with

myocardial infarction, there were certain aspects of this case which did not fit well with such a diagnosis. The severity of the initial symptoms and, especially, the height and duration of the fever would indicate a large area of infarction. If such were present an electrocardiogram made three days following the occurrence of the attack should certainly show characteristic changes. We should also expect distinct changes in the heart sounds, possibly a pericardial friction, persistent lowering of the blood pressure, and a greater degree of prostration than was exhibited by this patient. A diagnosis of dissecting aneurysm of the aorta seemed to fit the observed facts more closely. This case illustrates what would appear to be the minimum findings upon which the existence of a dissecting aneurysm could be surmised. The absence of electrocardiographic signs of coronary occlusion was an important diagnostic feature.

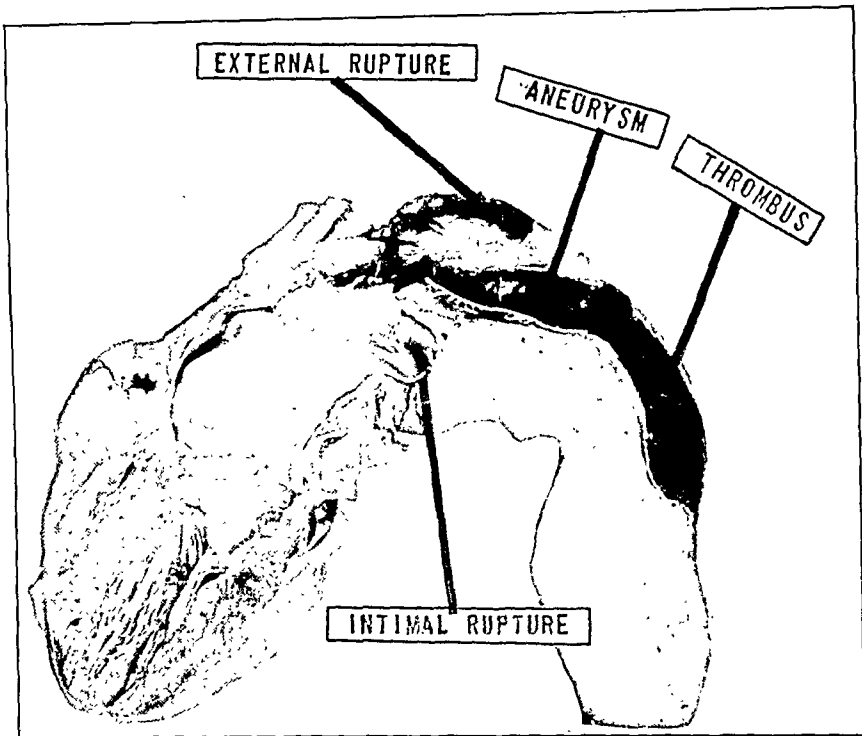


Fig. 3.—(Case 2) Intimal rupture at the isthmus, external rupture into the left pleural cavity.

CASE 3.—J. H. F., a man 43 years of age, was admitted to the Peralta Hospital on May 13, 1936, under the care of Dr. Charles F. Greenwood. I saw him in consultation on May 17. He had felt perfectly well previously, except that for about one week he had had to urinate once at night, and for about one month had had slight occipital headaches which were attributed to a refractive error. At 12:30 a.m., on May 13, he had, during sexual excitement, a sudden onset of gripping or constricting pain beneath the upper sternum which quickly passed downward through the chest and abdomen and, within a few minutes, to the back, apparently centering in the muscles along the spine, between the scapulae, and extending downward

into the lumbar region. In a half hour or so, a marked numbness of the left leg was noted, and with this an inability to move the left foot. The pain lessened for a short time, but within an hour became again very severe, so that one-half grain of morphine was required for relief. There was no headache or vomiting. The following morning, on his admittance to the hospital, the pain had abated somewhat. Vomiting had occurred twice, probably because of the morphine. Abdominal distention and rigidity, without tenderness, had developed. The left leg was perhaps not quite as warm as the right. The blood pressure was found to be 230/130. There was nothing else of note in the examination. During the next few days the distention was relieved with enemata. The numbness gradually disappeared from the left leg, passing off as a stocking is pulled off, but returned, for a while, the following day, in the left foot and lower third of the leg. Later, a "scalded" sensation was noted over the toes of the left foot, and also fairly severe cramplike pains in the anterior aspect of the left leg, with soreness in this region. On the morning of May 17 there was a localized area of acute tenderness in the midportion of the anterior surface of the left leg.

There had been no headache, vomiting, or diarrhea. The blood pressure had remained elevated despite the liberal use of nitrites. There had been a low-grade fever, not exceeding 100° F., and a leucocytosis of about 12,000, with 80 per cent polymorphonuclear cells. The urine was normal. The blood Wassermann and Kahn reactions were negative. There was radiographic evidence of a diffuse increase in the caliber and density of the aorta.

His personal medical history included evidence of a susceptibility to respiratory infections in childhood, and of questionable chorea at the age of 9 years. There had been some indefinite gastric disturbance between the ages of 25 and 27, while he was in China. Pyorrhea had been present and adequately treated one and a half years previously. A detailed family history was not available, but there was apparently a familial tendency to hypertension.

Examination at the time of the consultation, four days following the onset, revealed a well-developed and muscular man, apparently of his stated age, alert, co-operative, and not dyspneic or cyanotic or in obvious distress. The pupils reacted normally, the left being slightly irregular. The retinal arteries were somewhat constricted and definitely tortuous, particularly the secondary branches, but no hemorrhages or cotton-wool exudates were seen. The head and neck were otherwise normal. No abnormalities were found in the lungs or in the abdomen. The cardiac dullness was within normal limits. The action was forceful and regular, and the rate was a little rapid; a blowing systolic murmur of moderate intensity was heard at the apex. The blood pressure in the right arm was 196/124, and in the left, 220/140. The knee jerks were normal and equal, and no pathologic reflexes were obtained. The popliteal, dorsalis pedis and posterior tibial pulsations were not as strong in the left leg as in the right. He was unable to dorsiflex the left foot, to abduct it, or to extend the toes of this foot. The calf muscles and the extensors of the thigh were weak. The vibratory sense was normal. There was an area of anesthesia to touch, pain, and temperature covering the dorsum of the left great toe and the mesial half of the dorsum of the adjoining toe, extending upward upon the dorsum of the foot and converging to a point at about the level of the metatarsotarsal articulation. On the anterior surface of the middle portion of the left leg there was an area measuring about five centimeters transversely, by eight centimeters axially, which was red, slightly elevated, and tender to touch and pressure. The actual area of hyperesthesia corresponded roughly in size, shape, and position to the reddened area, but was slightly smaller and a trifle lower. Concentric with this there was a larger area, measuring about 8 x 10 centimeters, which was anesthetic to temperature. The fever lasted but a few days. The neurologic signs subsided gradually over a period of about two weeks. A few days subsequently bleeding

from the left kidney appeared without obvious cause, although infection later developed, possibly as a result of instrumentation. After the subsidence of the hematuria and pyelitis the patient returned to work and remained in fair health except for his hypertension, which slowly progressed. A roentgenogram of his chest, made two years following the acute attack, showed a diffuse widening of the aortic shadow which was more marked than it had been previously. It did not, however, show a double outline and could not be distinguished from a dilatation resulting from hypertension and arteriosclerosis.

In July, 1938, he began having some hematuria, and on a few occasions expectorated a little blood. On Aug. 12, 1938, he developed a severe headache and soon became unconscious. The spinal fluid was grossly bloody, and the clinical signs were those of subarachnoid hemorrhage. He died the following morning.

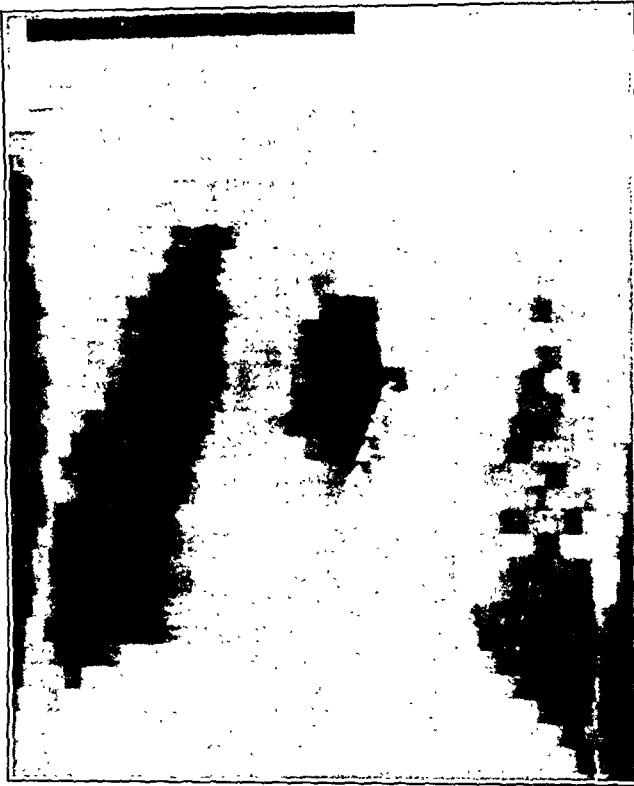


Fig. 4.—(Case 3) Roentgenographic and kymographic studies two years following onset show a broad aortic shadow indistinguishable from that caused by arteriosclerotic change.

Post-mortem examination, by Dr. Paul Michael, showed an old, healed, dissecting aneurysm which began at the level of the orifice of the left subclavian artery. Below this point the aorta was double until just above the bifurcation, where the true aortic channel became obliterated. The aneurysmal channel was larger than the true channel and surrounded the latter on the left and posteriorly, becoming more anterior in the abdominal portion. The lining of the aneurysm showed coarse longitudinal striation and numerous atheromatous plaques, especially in the abdominal portion. Microscopic examination revealed no endothelial lining. As the aneurysm passed downward, it had ruptured all of the intercostal and lumbar arteries on the left and had penetrated the left renal, the superior mesenteric, and the right iliac arteries. The true aortic channel supplied the right intercostal and lumbar arteries and the right renal artery. There was a small communication between the two

channels just anterior to the office of the left renal artery. Just above the bifurcation the true aortic channel became obliterated, and the aneurysm constituted the entire vessel. Rupture had, however, occurred into the left common iliac artery at its point of origin. The right common iliac was involved by the dissection as far as it was traced.

Associated pathologic findings were hypertrophy of the left ventricle, pleuritis on the left side, and bilateral nephrosclerosis. The central nervous system was not examined.

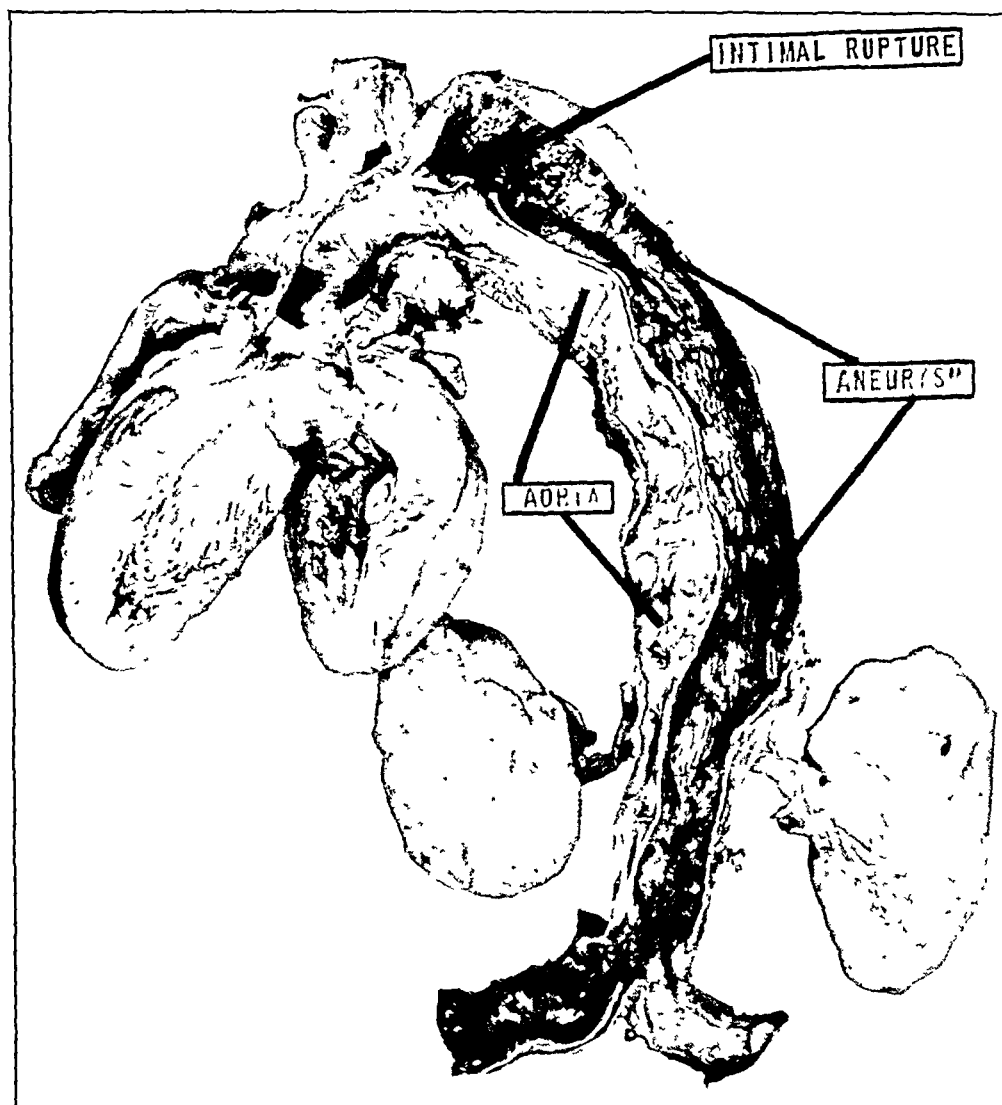


Fig. 5.—(Case 3) Intimal rupture at the isthmus, with double aortic channel. Obliteration of aorta just above the bifurcation by approximation of its walls. Single left iliac channel not involved by aneurysm. Large aneurysmal channel, and small, apparently functionless, true channel in right iliac artery.

Comment.—At the onset it was obvious that the patient had essential hypertension and that a circulatory accident had occurred, the exact nature of which was far less obvious. The presence of a dissecting aneurysm was strongly suspected, but it was thought that the pain and neurologic signs might also be the result of myelomalacia. After the ap-

pearance of the hematuria it seemed that only a dissecting aneurysm could produce all of the phenomena observed in this case. There were no manifestations which were inconsistent with such a diagnosis. Most dissecting aneurysms occur in males between forty and sixty years of age. There is usually a preceding hypertension. The onset is typically sudden, with pain and collapse, followed, if death does not ensue immediately, by fever and leucocytosis. The "wandering"¹⁰ pain felt by this patient, first anteriorly in the chest, then in the epigastrium, and later in the dorsal and lumbar regions, is characteristic of dissecting aneurysm involving the aortic arch and the descending aorta, although, as previously mentioned, it is not invariably present. The neurologic manifestations in the legs, which developed so quickly in this case, are of great diagnostic importance in association with evidence of a vascular accident within the chest. No such manifestations would be expected in connection with coronary occlusion, nor could the intense chest pain and collapse reasonably be ascribed to a primary spinal cord lesion. The absence of electrocardiographic evidence of myocardial infarction and the fact that the spinal fluid was normal were entirely consistent with the diagnosis of dissecting aneurysm. The circulatory changes in the legs developed gradually and were not intense. The converse is usually true of obstruction from a riding embolus. The occurrence of hematuria, easily explainable as the result of extension of a dissecting aneurysm into the renal artery, was exceedingly difficult to relate to the previously observed symptoms and signs by any other hypothesis. There was also significance in the fact that the blood came from the left kidney, that the neurologic signs were found on the left side, and that the circulatory changes were more marked in the left leg. This would be expected, in accordance with the anatomic relations described above, if the dissecting aneurysm passed down the descending thoracic and abdominal aorta posteriorly and a little to the left, involving the left renal artery. The feature of this case which was least consistent with a diagnosis of dissecting aneurysm was the recovery of the patient. Recovery may, however, sometimes occur, as a result either of thrombosis within the cavity of the aneurysm and organization of the thrombus, or of a second rupture through the intima of the aorta at the distal termination of the aneurysm. In the latter type, which is statistically more frequent, a double aortic channel is formed. The aneurysmal channel may become endothelialized. This type of healing could be surmised to have occurred in this case. The fairly rapid subsidence of the circulatory changes in the legs, and the absence of roentgenologic evidence of a double outline within the aortic shadow were more suggestive of re-entry of the aneurysm into the aorta than of healing by thrombosis. The extension of the aneurysm into the celiac axis and the superior mesenteric artery, which was found at the post-mortem examination, was not predicted.

SUMMARY

Reference to published accounts of thirty authentic cases of dissecting aneurysm of the aorta shows a rapid increase in the frequency with which the condition is being recognized. Three additional cases, in which the diagnosis was correctly made, illustrating the clinical features of the condition, are reported. One of these patients lived twenty-seven months after the acute attack. In this case it was possible to forecast the post-mortem finding of extension of the aneurysm into the left renal artery, and the presence of a double aortic channel. Since roentgenologic studies can only occasionally be of help in establishing the diagnosis, and the electrocardiogram is of value chiefly when it shows no signs of myocardial infarction, the chief reliance in diagnosis must be placed on clinical features. Patchy and bizarre neurologic changes in the legs, occurring as a result of circulatory deficiencies in the spinal cord from rupture of intercostal and lumbar arteries by a dissecting aneurysm, are of great diagnostic importance. Hematuria or anuria, in association with evidences of a circulatory accident within the chest, are also important as indicative of involvement of one or both renal arteries by an aneurysm. Attention to the clinical features should enable the diagnosis to be made with still greater frequency.

REFERENCES

1. Nicholls, Frank: Some Observations on Aneurysms in General. *Philosophical Transactions of the Royal Society, London* 35: 440, 1728-29.
2. Swaine, Keyworth, and Latham, P. M.: A Case of Dissecting Aneurysm of the Aorta, *Trans. Path. Soc. London* 7: 106, 1856.
3. Shennan, T.: Medical Research Council Special Report Series No. 193. London. His Majesty's Stationery Office. 1934.
4. (a) Hirschbeck, F. J., and Boman, P. G.: A Case Report of Dissecting Aneurysm of the Aorta With Distinctive X-ray Findings, *Minnesota Med.* 5: 724, 1922 (one case).
- (b) Samson, Paul C.: Dissecting Aneurysm of the Aorta, Including the Traumatic Type: Three Case Reports, *Ann. Int. Med.* 5: 117, 1931 (One case, diagnosis made by Dr. Roger T. Vaughan).
- (c) Kellog, F., and Heald, A. H.: Dissecting Aneurysm of the Aorta. Report of a Case Diagnosed During Life, *J. A. M. A.* 100: 1157, 1933 (one case).
- (d) Lounsbury, J. B.: Clinical Symptoms and Signs of Dissecting Aneurysm With Report of a Case Diagnosed During Life, *Yale J. Biol. and Med.* 7: 209, 1935 (one case).
- (e) Weiss, Soma: Clinical Course of Spontaneous Dissecting Aneurysm of the Aorta, *M. Clin. North America* 18: 1117, 1935 (one case).
- (f) Gurin, D., Blumer, J. W., and Derby, R.: Dissecting Aneurysm; Diagnosis and Operative Relief of Acute Arterial (Iliac and Femoral) Obstruction Due to This Cause, *New York State J. Med.* 35: 1200, 1935 (one case).
- (g) Löffler, W.: Zur Klinik und Diagnostik der Aortenruptur, *Schweiz. med. Wchnschr.* 16: 790, 1935 (three cases).
- (h) Osgood, E. F., Gourley, M. F., and Baker, Russel L.: Diagnosis of Dissecting Aneurysm of the Aorta, *Ann. Int. Med.* 9: 1398, 1936 (two cases).
- (i) Glendy, Robt. E., Castleman, Benjamin, and White, Paul D.: Dissecting Aneurysm of the Aorta: A Clinical and Anatomical Analysis of Nineteen Cases (Thirteen Acute) with Notes on the Differential Diagnosis, *AM. HEART J.* 13: 129, 1937 (two cases).
- (j) Roesler, H., Gifford, U. G., and Betts, W.: Dissecting Aneurysm of the Aorta Correctly Diagnosed, with Description of a Sign Heretofore not Mentioned, *AM. HEART J.* 13: 426, 1937 (one case).

- (k) McGeachy, T. E., and Paullin, J. E.: Dissecting Aneurysm of the Aorta, J. A. M. A. 108: 1690, 1937 (three cases).
- (l) Blackford, L. Minor, and Smith, Carter: Coronary Thrombosis vs. Dissecting Aneurysm in Differential Diagnosis, J. A. M. A. 109: 262, 1937 (one case).
- (m) Middleton, Wm. S., and Porter, Reno R.: Diagnosis of Spontaneous Dissecting Aneurysm of the Aorta, Trans. Ass'n. Am. Physicians 52: 67, 1937 (one case).
- (n) Boyd, Linn L., and Werblow, Chas. S.: Coarctation of the Aorta, Dissecting Aneurysm and Aneurysmal Dilatation of the Left Vertebral Artery: Report of a Case, Ann. Int. Med. 11: 845, 1937 (one case).
- (o) Leik, D. W.: Diagnosis of Dissecting Aneurysm with Report of a Case, J. Iowa State Med. Soc. 28: 13, 1938 (one case).
- (p) Claiborne, T. S., and Holler, Emory D.: Dissecting Aneurysm of the Aorta and Course for Fifty-three Days, AM. HEART J. 15: 358, 1938 (one case).
- (q) Hamberger, Morton, Jr., and Ferris, Eugene B., Jr.: Dissecting Aneurysm: A Study of Six Recent Cases, AM. HEART J. 16: 1, 1938 (two cases).
- 5. Keinbock, Robert, and Weiss, Konrad: Ein Fall von Aneurysma dissecans der Brustaorta, Fortschr. a. d. Geb. d. Röntgenstrahlen 44: 211, 1931.
- 6. (a) Kalischer: Aneurysma dissecans der Aorta mit Paraplegie, Berliner klin. Wchnschr. 51-2: 1286, 1914.
- (b) Pannhorst, R.: Symptomatologie und Diagnose der Aortenruptur und des Aneurysma dissecans, Deutsches Arch. klin. f. Med. 175: 115, 1933.
- 7. (a) Perry, Thomas M.: Dissecting Aneurysms of the Aorta With a Report of Five Cases, AM. HEART J. 12: 650, 1936.
- (b) Glendy, Castleman, and White, loc. cit.
- 8. Krukenberg, Ernst: Beiträge zur Frage des Aneurysma dissecans, Beitr. z. path. Anat. u. z. allg. Path. 67: 329, 1920.
- 9. Tyson, M. Dawson: Dissecting Aneurysms, Am. J. Path. 7: 581, 1931
- 10. Löffler, loc. cit.

CONGENITAL HEART DISEASE IN CHILDHOOD, WITH SPECIAL REFERENCE TO PROGNOSIS

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WITHIN recent years the subject of congenital cardiac defects has aroused increasing interest, inspired in great part by the efforts of Dr. Maude E. Abbott to clarify the differential diagnosis through the analysis of case reports and of pertinent clinical and laboratory studies. Under the stimulus of her interest, moreover, information concerning the incidence at autopsy of such congenital defects has been assembled from various hospitals in the United States and Canada (Table I).¹

The present paper is based on an analysis of the records of all children with congenital cardiac defects admitted to the wards or cardiac clinic of the Children's Hospital during the years 1922 to 1936, inclusive. Since we were interested not only in the incidence of congenital cardiac lesions but also in their prognostic significance, the effort was made during the first six months of 1938 to trace and bring back for examination all children not under current observation.

During these fifteen years 230 children with a presumptive diagnosis of congenital defect were seen at the Children's Hospital. In infancy the diagnosis was based on the existence of an intense murmur not associated with marked anemia. In older children a congenital lesion was suspected when a murmur was heard best at sites not characteristic of the acquired valvular lesions (Table II). In 36 cases (15.6 per cent) a thrill was palpated. At all ages the diagnosis was frequently aided by the roentgenologic finding of cardiac enlargement or change in contour, or by abnormalities noted in the electrocardiogram. Persistent cyanosis was present in 67 of the 217 children who were 2 years of age, or older; clubbing of the fingers was seen in 16 cases.

In one-half of the cases, the patients were first seen when they were infants (Table III). The existence of a cardiac defect was noted elsewhere during the first months of life in thirty children who later came under observation at the Children's Hospital. The diagnosis of a congenital lesion was therefore made early in infancy in 64 per cent.

In the total group of 230, 117 were boys (50.9 per cent) and 113 girls (49.1 per cent). Fifty-one were negroes (22.2 per cent) and

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Read before the Philadelphia Pediatric Society, Jan. 10, 1939.

Received for publication Dec. 14, 1938.

TABLE I
COMPARATIVE INCIDENCE OF CONGENITAL CARDIAC DEFECTS FOUND AT NECROPSY

	TOTAL NUMBER AUTOPSIES	CONGENITAL HEART DISEASE		AUTOPSIES NEONATAL PERIOD		AUTOPSIES 1-2 YEARS		AUTOPSIES 2 YR.—ADULT		CHILDREN OVER 2 YEARS	
		NO.	PER CENT	NO.	PER CENT CONGENITAL HEART DISEASE	NO.	PER CENT CONGENITAL HEART DISEASE	NO.	PER CENT CONGENITAL HEART DISEASE	NO.	PER CENT CONGENITAL HEART DISEASE
Leech—Baltimore Johns Hopkins Hospital	13,115	170	1.29								
Terplan and Sanes Buffalo General Hospital	336	21	6.3								
Philpott Montreal Hospitals	7240	80	1.1	759	4.7	957	2.8	5522	0.3		
Nicholson—Washington, D. C. Pediatric Service—four hospitals	1851	37	2.0								
McGinn—Boston Massachusetts General Hospital	7500	67	0.9	70	10.0	146	4.6			2159	0.8
Ramek and Propst—Philadelphia University of Pennsylvania Hospital	4255	36	0.85	398	1.75	223	4.95	3034	0.52		
Szypulski—Philadelphia Philadelphia General Hospital	7500	111	1.4	157	4.4	184	13.04	7159	1.1		
Gibson and Clifton—Chicago Children's Memorial Hospital	1950	105	5.4								
Present series—Philadelphia Children's Hospital	1075	34	3.16	116	3.45	710	3.94			236	0.89

TABLE II

SITES AT WHICH MURMURS WERE BEST HEARD IN 230 CASES OF CONGENITAL CARDIAC ANOMALY

LOCATION OF MURMUR	NUMBER OF CASES
First and second left interspaces	55
Third left interspace	27
Below left clavicle and at fourth left interspace	50
Fourth interspace, left of sternum	48
First to third right interspaces	3
Diffuse precordial, no localization	32
No murmur	15

TABLE III

AGE WHEN FIRST SEEN IN 230 CASES OF CONGENITAL CARDIAC ANOMALY

AGE IN YEARS	NUMBER OF CASES
Under 1	117
1	30
2-4	35
5-9	30
10-12	18

179 white (77.8 per cent). Information concerning 189 (80.2 per cent) was obtained in 1938 (Table IV). Of the 41 children who could not be located, 28 had attained the age of at least 2 years when they were last seen, so that the course in the first two years is known in 217 instances, or 94.3 per cent of the group (Tables V and VI).

TABLE IV

PROGNOSIS IN 230 CASES OF CONGENITAL CARDIAC DEFECT

FIRST ADMISSION	TOTAL NO. PATIENTS	PATIENTS TRACED		DEATHS		LIVING PATIENTS, AGED 2 OR MORE; FUNCTIONAL CLASSIFICATION*		
		NO.	PER CENT	NO.	PER CENT	I	Ia	Ib
Wards	131	112	85.5	86	66.5	23	6	6
Clinic	99	77	77.7	16	20.8	66	9	4
Total group	230	189	82.2	102	53.9	89	15	10

*The functional classification is based on the "Criteria" of the American Heart Association. I indicates physical activity not limited; Ia, activity slightly limited; Ib, activity greatly limited. All individuals in Class Ib and 5 in Class Ia were cyanotic. Two individuals in Class Ia and 6 in Class I had suffered transient attacks of cyanosis in infancy.

TABLE V

AGE OF LIVING PATIENTS WHEN LAST SEEN

AGE IN YEARS	BORN SINCE 1922		BORN BEFORE 1922		TOTAL	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
2-4	20	23.8	5	16.1	25	21.7
5-9	26	30.9	4	12.9	30	26.1
10-14	26	30.9	5	16.1	31	26.9
15-26	12	14.4	17	54.9	29	25.3
Total	84	100.0	31	100.0	115	100.0

TABLE VI
AGE AT DEATH

AGE IN YEARS	CYANOTIC*		NONCYANOTIC		TOTAL	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Under 6/12	35	50.0	8	25.0	43	42.1
6/12-1	20	28.6	12	37.5	32	31.4
2-4	5	7.1	8	25.0	13	12.7
5-9	6	8.6	2	6.25	8	7.8
10-19	4	5.7	2	6.25	6	6.0
Total	70	100.0	32	100.0	102	100.0

*Includes all types of cyanosis: 47, persistent; 3, recurrent; 16 terminal.

DEATHS

The total number of deaths was 102 (53.9 per cent of those traced in 1938, and 47 per cent of those who were 2 years of age, or older, when they were last examined). Half of the deaths occurred among boys and half among girls. In 20 per cent of the cases the children were negroes.

Eighty-four per cent of all deaths occurred among the children who had been seen first in the wards. The majority of these, when first seen, had presented symptoms of serious illness. Eighteen patients were moribund on admission. Sixteen per cent of the deaths occurred among the patients who came originally to the cardiac clinic. In many of these the lesion had been discovered accidentally during routine examination. Eighty per cent of the children first seen in the clinic had never required hospitalization, if admissions for tonsillectomy were excluded.

The death rate on the wards had been 70.6 per cent for infants below the age of one year. Of the 72 children who had been admitted as babies, 91.6 per cent were dead in 1938. Of the 42 infants who had originally come under observation in the cardiac clinic, one-third had died. Among the 94 children who had reached school age, the incidence of deaths was 11 per cent.

Seventy-three per cent of the deaths had occurred within the first year of life, and 78 per cent within the first two years (Table VI). In Baltimore,^{1a} 75 per cent of the deaths in children with congenital cardiac anomalies took place within the first year. Half of the deaths in Irvine-Jones' series² occurred below the age of six months.

Deaths Among Individuals Born Since 1922.—Since the majority of deaths had occurred in the first 2 years of life, the inclusion of individuals born prior to 1922, who had come under observation after safely weathering the period of infancy, would tend to lower the death rate artificially. We have, therefore, made a separate analysis of those born during the years 1922-1936, comprising 191 children, 93.7 per cent of whom had been followed at least until their second birthday (Table VII). There were 95 deaths (53 per cent).

TABLE VII
PROGNOSIS ACCORDING TO AGE (INDIVIDUALS BORN SINCE 1922)

AGE YR.	NO. OF CASES	NUMBER TRACED	DEATHS		DEATHS	
			NO.	PER CENT	CYANOTIC GROUP* PER CENT	NONCYANOTIC PER CENT
1	191	183	59	37.7	50.0	24.8
2	191	178	79	44.4	63.4	32.6
5	151	138	68	49.4	78.5	36.4
10	102	81	37	45.7	73.7	37.1

*In the cyanotic group were placed only individuals with continuous cyanosis or persistent recurrent attacks. Individuals with transient cyanosis early in life, or those who presented terminal cyanosis were considered noncyanotic.

Cause of Death.—In slightly over one-half of the cases (52.9 per cent) the final illness was of infectious origin. Pneumonia headed the list of infections, causing 39 per cent of the deaths. Bacterial endocarditis was the terminal event in only two cases. Three deaths were due to each of the following: acute meningitis, septicemia, tuberculosis, and acute gastroenteritis. In one-third of the deaths circulatory inadequacy was a prominent feature. There were two instances of sudden death without preceding symptoms. The first occurred in an infant with heart block; the second, in a nine-year-old girl with aortic stenosis (diagnosis proved by necropsy) who fell dead following a blow over the precordial region received in a childish quarrel.

Of the 38 patients who came to necropsy, there were 10 children in whom no cause of death could be found other than circulatory failure. All were cyanotic. Of 17 patients belonging to the acyanotic, or late cyanotic, groups, according to Dr. Abbott's classification,³ 15, or 88.2 per cent, died of infection, and 1, or 6 per cent, of circulatory failure. A previously mentioned child with aortic stenosis died suddenly. Of 21 patients belonging to the cyanotic group, 57 per cent died of infection and 43 per cent as a result of the cardiac defect itself.

INFLUENCE OF CYANOSIS ON PROGNOSIS

Fifty-six per cent of the children—80 per cent of the living individuals and 30 per cent of those that had died (Table VIII)—had never been cyanotic. The death rate of the cyanotic infants during the first year of life was twice that of the noncyanotic, and rose progressively with age as the children gradually succumbed to infection or circulatory failure (Fig. 1). After the second year of life there was a marked drop in deaths among the noncyanotic individuals. Among 94 children who had attained the age of six years, or over, 13 were cyanotic. Eighty per cent of these cyanotic school children were dead at the end of the period of observation, whereas only 5 per cent of the noncyanotic school children had died.

The prospect for the cyanotic victims of congenital cardiac defects is not very hopeful. In the present series, of 16 individuals with

persistent cyanosis who reached the age of 5 years, 10 were leading lives of greatly restricted activity. Of the 7 who reached the age of 10 years, 4 were cardiac cripples. Four children lived past their fifteenth birthday. One has since died; two have always been incapable of much exertion.

TABLE VIII

INCIDENCE OF CYANOSIS IN 217 INDIVIDUALS TWO YEARS OF AGE, OR OLDER

	BORN SINCE 1922				BORN BEFORE 1922				TOTAL	
	LIVING		DEAD		LIVING		DEAD		NO.	PER CENT
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT		
No cyanosis	66	78.5	29	30.5	25	80.8	1	14.3	121	55.8
Persistent	10	11.9	47	49.5	6	19.2	4	57.1	67	30.9
Recurrent in early life	8	9.6	3	3.2	0	0.0	1	14.3	12	5.5
Terminal	0	0.0	16	16.8	0	0.0	1	14.3	17	7.8
Total	84	100.0	95	100.0	31	100.0	7	100.0	217	100.0

In an occasional instance, however, the outlook is by no means hopeless. There was the talented musician with the tetralogy of Fallot who died in his sixtieth year;⁴ the woman, 62 years of age, working as a librarian, without complaints other than of cyanosis;⁵ and the cyanotic laborer who lived to his forty-first year, dying not of any cardiac disturbance, but of uremia due to chronic glomerulonephritis.⁶

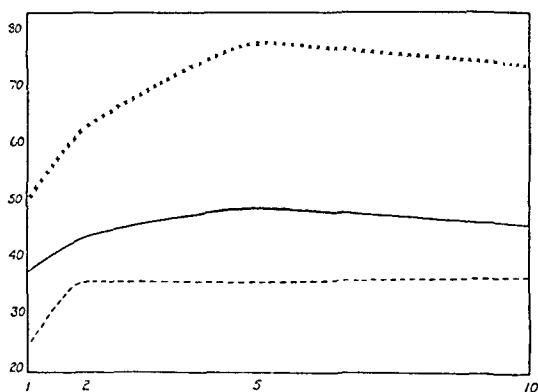


Fig. 1.—Percentage of deaths among children with congenital cardiac anomalies born during the years 1922 to 1936. The dash line indicates the noncyanotic individuals; the crosses, the cyanotic individuals; the solid line, the total group. Only individuals with continuous cyanosis or persistent recurrent attacks were placed in the cyanotic group. Individuals with transient cyanosis in early life or those who presented cyanosis as a terminal phenomenon were placed in the noncyanotic group. The numbers at the bottom represent age in years, those at the side, percentage of deaths.

Cyanotic women have given birth to normal children.⁷ Snellings⁸ mentions the case of a man, 54 years of age, cyanotic from birth, as were his mother and grandmother, himself the father of three children, two of whom were cyanotic because of congenital heart disease.

The oldest cyanotic individual in the present series is a boy, 21 years of age, intelligent and with many interests, attending a technical school to which he had been granted a scholarship. Six years ago, this boy's erythrocyte count was 9,000,000, and his hemoglobin 150 per cent, which would seem to controvert the statement of Vaquez and Quiserne, quoted by Abbott,⁹ that a count above 6,000,000 is always of grave prognostic import. In our group of living cyanotic children the average of 20 erythrocyte counts was 7,390,000, the average hemoglobin was 118 per cent, the maximum erythrocyte count 11,180,000, and the maximum hemoglobin 165 per cent. Of the cyanotic individuals that died, the average of 25 erythrocyte counts was 5,380,000, the average hemoglobin was 90 per cent, the maximum erythrocyte count 7,820,000, and the maximum hemoglobin 128 per cent.

Cyanosis preceded the appearance of clubbing by varying intervals of time. Clubbing of the fingers occurred in 16 individuals, the youngest being 4 months of age. In two cyanotic children, aged 10 and 16 years, respectively, the fingers were not clubbed.

OTHER ASSOCIATED ANOMALIES

Mental Deficiency.—Eighteen children (7.8 per cent) were Mongolian idiots. Three children were microcephalic. Two others were inmates of institutions for the feeble-minded. Eight children, enrolled in the public schools, had been placed in "orthogenic backward" classes maintained for pupils with intelligence too low to enable them to keep up with the regular curriculum. In addition, three children below school age were mentally retarded. There were, thus, 34 children (14.5 per cent) with retarded mental development. The question may be raised whether such mental deficiency is due to a primary cerebral defect or is secondary to inadequate cerebral circulation. There is little doubt of the congenital origin of the cerebral abnormalities in Mongolian idiocy and in microcephaly. The most plausible assumption would be that in the remaining 13 children some form of cerebral aplasia was present.

Eighteen individuals presented associated defects other than cerebral maldevelopment. One of these, in addition, was microcephalic, and three were Mongolian idiots. In all, including the Mongolian idiots and microcephalics, there were 35 cases of associated congenital defect (10.9 per cent).

CLINICAL ASPECTS

Infants with congenital cardiac defects tend to be slow to gain weight and delayed in growth. Malnutrition of a degree sufficient to be noted in the clinical records was present in 69 children (30 per cent) of the present group. The marasmus of many of the infants admitted to the wards undoubtedly helped bring about the high mortality rate. In later life these children may remain dwarfed and of

fragile build. In some individuals, however, a spurt of growth occurs as puberty is reached.

Mental deficiency is a not infrequent occurrence, particularly among the noncyanotic individuals.

In infancy and early childhood, increased susceptibility to infections, especially respiratory, is common. Pneumonia, although a frequent cause of death, is not invariably fatal. It is known that 23 of our children (one cyanotic) survived attacks of pneumonia. Several individuals suffered repeated illnesses in early life, associated with signs of pulmonary involvement. Since there was a high incidence of lipid pneumonia among the patients examined post mortem, it is possible that some of these children with long-continued pneumonia in early childhood had recovered from lipid pneumonia. No death occurred from any of the infectious diseases common to childhood, including pertussis in 11 cases. Eight children had suffered from rheumatic infection.

Operative procedures were well borne, including 33 tonsillectomies and adenoidectomies (two in cyanotic individuals), one splenectomy, one mastoidectomy, one herniorrhaphy, and one open reduction for subluxation of the elbow. Death due to peritonitis followed laparotomy in a case of appendiceal abscess. In a marasmic infant, anoplasty for imperforate anus with rectovaginal fistula was followed by death from septicemia.

There are many instances of longevity among noncyanotic individuals with congenital cardiac defects, but, on the whole, the prognosis is poor for the cyanotic individual. However, since a few of them have lived long and useful lives, it is unfair to assume a hopeless prognosis in any child who has survived infancy. Cyanotic children should not be deprived of schooling.

Whether cyanosis is present or absent, there is no indication for exercise restriction beyond the limiting capacity of the heart itself. Children with congenital lesions are more fortunate than their rheumatic brothers and sisters in that they do not have the additional handicap of continued systemic and myocardial infection. In spite of startling murmurs and cardiac enlargement, the functional capacity is often normal (Table IV).

SUMMARY

A review has been made of 230 records of children with congenital cardiac defects seen at the Children's Hospital during the years 1922 to 1936. Information concerning 80 per cent of this group was obtained in 1938. One hundred two children had died, 73 per cent of the deaths occurring within the first year of life. The death rate among infants with symptoms serious enough to warrant admission to the hospital was as high as 70 per cent. One-third of the infants

who came originally under observation in the cardiac clinic had died during the period of observation. Of 94 school children, 11 per cent had died. The mortality rate observed among groups of children with congenital cardiac defects will thus be greatly influenced by the selection of patients. Impressions derived from experience with school children will be unduly optimistic.

The death rate of cyanotic infants was twice that of noncyanotic, and continued to rise progressively with age, whereas that of noncyanotic individuals tended to show only a slow increase after the second year of life.

One-half of all deaths were due to infection, with pneumonia heading the list. Among the patients that came to necropsy, 90 per cent of those with lesions of the acyanotic and delayed cyanotic type had died of infection, whereas 40 per cent of individuals with lesions of the cyanotic type had died of the cardiac defect itself.

We wish to acknowledge our indebtedness to Dr. Arthur D. Waltz and Dr. Irving J. Wolman for the privilege of reviewing the post-mortem records; and to Miss Hilda Smith and Miss Letitia Scott, without whose aid many of these children could not have been traced.

REFERENCES

1. a. Leech, C. B.: Congenital Heart Disease, *J. Pediat.* 7: 802, 1935.
 b. Terplan, K., and Sanes, S.: The Incidence of Congenital Heart Lesions in Infancy. A Comparative Statistical Study Based on Postmortem Examinations, *J. Tech. Methods* 15: 86, 1936.
 c. Philpott, N. W.: Relative Incidence of Congenital Anomalies in Montreal Hospitals, *J. Tech. Methods* 15: 96, 1936.
 d. Nicholson, M. M.: Relative Incidence of Cardiac Anomalies Found in Autopsies Performed in Washington Hospitals, *J. Tech. Methods* 15: 100, 1936.
 e. McGinn, S.: Incidence and Progress in the Recognition of Congenital Heart Disease in the Massachusetts General Hospital, *J. Tech. Methods* 16: 98, 1936.
 f. Ramek, H. W., and Propst, J. H.: Incidence of Congenital Cardiac Anomalies Found at Autopsies Performed in the Hospital of the University of Pennsylvania, *J. Tech. Methods* 17: 113, 1937.
 g. Szypulski, J. T.: A Study of Congenital Heart Disease at the Philadelphia General Hospital, *J. Tech. Methods* 17: 119, 1937.
 h. Gibson, S., and Clifton, W. M.: Congenital Heart Disease. A Clinical and Postmortem Study of One Hundred and Five Cases, *Am. J. Dis. Child.* 55: 761, 1938.
2. Irvine-Jones, E. I. M.: A Clinical Study of Congenital Heart Disease in Childhood, *AM. HEART J.* 2: 121, 1927.
3. Abbott, M. E., and Dawson, W. T.: The Clinical Classification of Congenital Cardiac Disease, *Internat. Clin.* 4: 156, 1924.
4. White, P. D., and Sprague, H. B.: The Tetralogy of Fallot. Report of a Case in a Noted Musician Who Lived to His Sixtieth Year, *J. A. M. A.* 92: 787, 1929.
5. McGinn, S., and White, P. D.: Progress in the Recognition of Congenital Heart Disease, *New England J. Med.* 214: 763, 1936.
6. Volini, I. F., and Flaxman, N.: Tetralogy of Fallot: Man Who Lived to His Forty-First Year, *J. A. M. A.* 111: 2000, 1938.
7. a. Easby, M. H.: Early Recognition of Cardiac Insufficiency in Presence of Pregnancy, *M. Clin. North America* 21: 1059, 1937.
 b. Townsend, C. W.: Congenital Heart Disease. Study of 30 Cases, *Arch. Pediat.* 16: 680, 1899.
8. Burwinkle, quoted by Snelling, D. B.: Familial Congenital Heart Disease, *J. A. M. A.* 108: 1502, 1937.
9. Abbott, M. E.: *Bedside Diagnosis*, p. 458, G. Blumer, Editor, Philadelphia, 1928, W. B. Saunders Company.

COMPARATIVE EFFECTS OF AMPHETAMINE SULFATE (BENZEDRINE SULFATE), PAREDRIE, AND PROPADRINE ON THE BLOOD PRESSURE

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ONE of the characteristic actions of benzedrine sulfate (phenylisopropylamine or amphetamine sulfate), a sympathomimetic amine, is to increase the blood pressure for a comparatively long period of time. For this purpose other closely related amines may prove to be as effective as, or more effective than, benzedrine sulfate. In this study, two other amines, paredrine (3-parahydroxyphenylisopropylamine) and propadrine (phenylpropanolamine hydrochloride), are compared to benzedrine sulfate in respect to their action on the blood pressure and pulse rate.

Paredrine, like benzedrine, has been noted by Alles¹ to be the most intensely active of the amines which show any appreciable degree of activity when given by mouth. Unlike benzedrine, however, its action appears to be confined practically entirely to the peripheral sympathetic mechanisms. The only previous clinical study of this drug was carried out by Abbott and Henry,² who found that the drug is one-fiftieth as potent as epinephrine, if given subcutaneously, and about twice as potent as ephedrine when given by mouth. With oral administration, in doses of 10 to 40 mg., these authors noted a rise in systolic blood pressure ranging from 24 to 100 mm. Hg. When given subcutaneously in doses of 10 and 40 mg., a rise in systolic blood pressure of 20 to 96 mm. Hg was observed. There was noted regularly a diminution in pulse rate with the rise in blood pressure. No definite central effects occurred following administration of the drug. The following symptoms were occasionally noted: palpitation, constriction across the chest, sweating, and mild headache.

Very little work has been done clinically with propadrine. It has been used in the treatment of allergic manifestations by Black³ and by Boyer.⁴ Chen and his co-workers⁵ administered the drug orally in 50 mg. doses to two individuals and noted rises of 16 and 30 mm. Hg, respectively, in the systolic blood pressure. We are unable to find any clinical observations which have been made following the intravenous administration of either paredrine or propadrine.

From the Division of Psychiatric Research, Boston State Hospital, Boston, aided by grants from the Commonwealth of Massachusetts and the Rockefeller Foundation.
Received for publication Dec. 15, 1938.

In a recent unpublished study⁶ we observed that paredrine and propadrine, in contrast to benzedrine, have little central stimulating

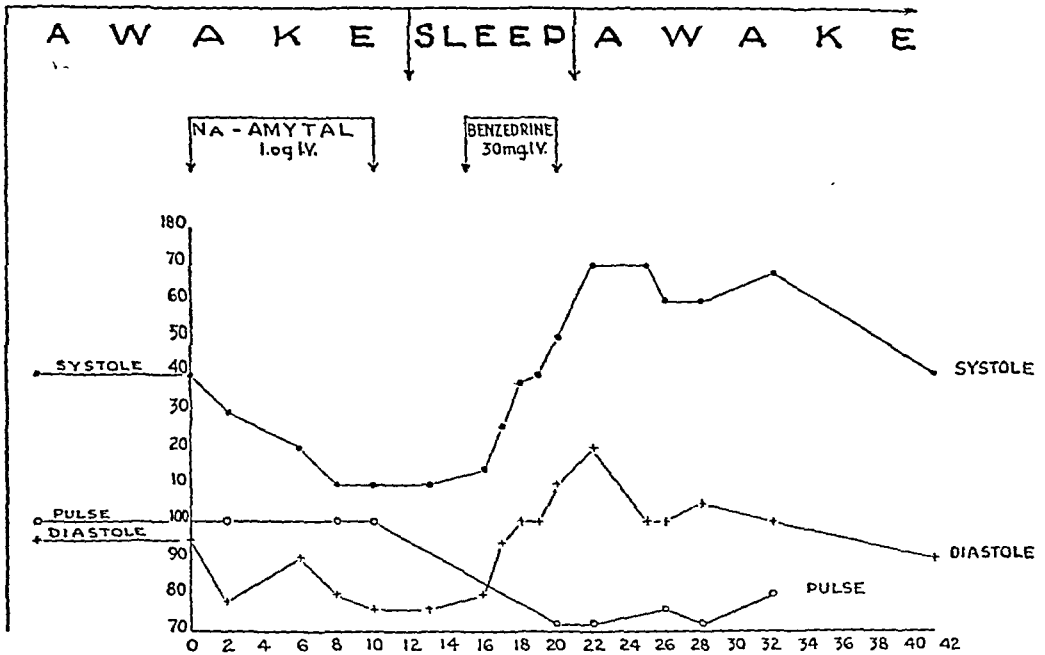


Fig. 1.—Effect of benzedrine sulfate on the narcosis induced by sodium amytal.* The patient awoke within two minutes after the end of the injection of benzedrine.

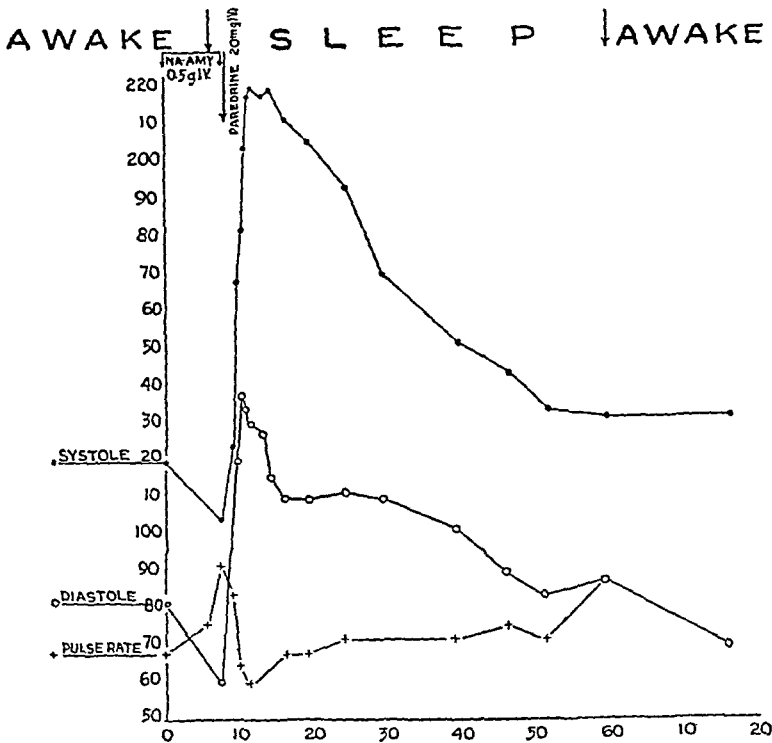


Fig. 2.—Typical effect of the administration of paredrine following administration of sodium amytal. The paredrine had no influence on the narcosis even though the blood pressure rose to a very high level following the paredrine injection.

*All drugs injected intravenously.

action, as indicated by their effects on the narcosis produced by sodium amytal (Figs. 1, 2, and 3). The counteracting effect of benzedrine on the narcosis of sodium amytal has also been noted by Reifenstein and Davidoff.⁷

A group of subjects were given intravenous injections of benzedrine in doses of 20 mg., paredrine in doses varying from 5 to 20 mg., and propadrine in doses varying from 20 to 50 mg.

Effect of Benzedrine (Ten Subjects, Table I).—Within two to fourteen minutes following intravenous injections of 20 mg. of benzedrine, the blood pressure reached its maximum, the increase varying from 30 to 56 mm. Hg. After reaching its peak, it gradually fell to its original level in 40 to 94 minutes. The pulse rate during the increase in blood pressure either remained essentially unchanged or slowed. The greatest diminution in pulse rate was 20 beats per minute. In none of the cases was any change in cardiac rhythm noted.

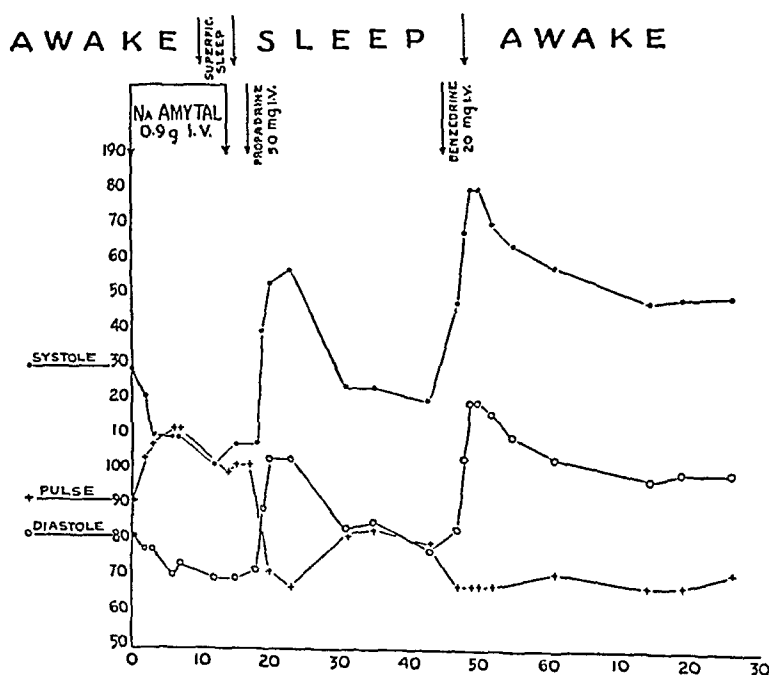


Fig. 3.—Effect of administration of propadrine following the injection of sodium amytal. The propadrine had no influence on the narcosis.

Effect of Paredrine (Ten Subjects, Table II).—Three of the ten subjects were given 20 mg. of paredrine intravenously. Because the systolic blood pressure rise was very great in these cases, namely, 56, 102, and 118 mm. Hg, respectively, smaller doses, varying from 5 to 15 mg., were employed in the other cases. With these doses the rise in systolic blood pressure varied from 28 mm. to 88 mm. Hg. The blood pressure reached a maximum in two to twelve minutes, returning to its original level in twenty to seventy minutes. In nine cases

the pulse rate became slower, the greatest change coinciding with the maximum blood pressure reading. The slowing of pulse rate varied from 4 to 32 beats per minute. In the tenth case a rise of 6 beats per minute occurred. No cardiac arrhythmias were noted in any case.

TABLE I

EFFECT OF INTRAVENOUS ADMINISTRATION OF BENZEDRINE SULFATE ON BLOOD PRESSURE AND PULSE RATE

CASE	DOSE MG.	CONTROL PERIOD		HEIGHT OF REACTION		TIME (MINUTES)
		BLOOD PRESSURE	PULSE RATE	BLOOD PRESSURE	PULSE RATE	
A. F.	20	102/68	60	150/84	60	60
E. B.	20	116/74	60	152/84	60	60
J. F.	20	130/90	74	180/110	68	40
N. K.	20	142/90	76	194/110	58	54
R. C.	20	116/70	70	148/70	68	66
E. F.	20	110/70	76	166/96	66	94
E. F.	20	118/70	76	148/96	74	74
E. J.	20	120/80	80	160/90	72	80
E. H.	20	130/70	88	178/100	68	70
E. K.	20	146/100	68	190/110	54	62

TABLE II

EFFECT OF INTRAVENOUS ADMINISTRATION OF PAREDINE ON BLOOD PRESSURE AND PULSE RATE

CASE	DOSE MG.	CONTROL PERIOD		HEIGHT OF REACTION		TIME (MINUTES)
		BLOOD PRESSURE	PULSE RATE	BLOOD PRESSURE	PULSE RATE	
M. W.	10	122/74	88	172/100	56	58
T. F.	10	130/68	92	174/100	60	45
J. V.	20	114/60	92	170/80	60	38
E. F.	7.5	100/44	48	160/100	40	70
E. B.	15	100/82	64	198/100	52	35
E. F.	15	100/60	44	170/105	50	65
T. F.	20	118/68	72	220/90	52	70
A. F.	5	92/66	72	120/76	64	20
M. B.	15*	116/60	68	136/66	60	70
J. V.	20*	100/60	80	218/70	76	62

*By intramuscular route.

Effect of Propadrine (Twelve Subjects, Table III).—Eight of these subjects received 50 mg., and the other four, doses varying from 20 to 25 mg. The rise in systolic blood pressure in those receiving the larger doses varied between 44 and 82 mm. Hg. In three subjects who received the smaller dose, a rise in blood pressure of 16, 16, and 28 mm. Hg, respectively, occurred. In the last case no change in blood pressure occurred. The blood pressure reached its maximum one to seven minutes following the injections, and gradually fell to original levels in thirty to ninety-five minutes. The pulse diminished in rate in every case, the decrease ranging from 16 to 36 beats per minute. There was no disturbance in cardiac rhythm in any case.

TABLE III

EFFECT OF INTRAVENOUS ADMINISTRATION OF PROPADRINE ON BLOOD PRESSURE AND PULSE RATE

CASE	DOSE MG.	CONTROL PERIOD		HEIGHT OF REACTION		TIME (MINUTES)
		BLOOD PRESSURE	PULSE RATE	BLOOD PRESSURE	PULSE RATE	
M. B.	50	112/70	68	194/102	42	76
J. H.	50	116/62	88	174/106	60	80
A. McN.	50	94/62	84	160/100	48	60
T. F.	50	108/60	56	174/90	36	95
E. B.	50	116/82	64	190/100	44	90
J. V.	50	106/66	92	150/80	72	40
J. V.	25	114/70	88	130/84	72	30
M. W.	50	134/86	92	200/116	56	82
R. C.	25	116/64	68	140/80	52	46
M. B.	50	110/58	64	188/104	48	62
M. W.	20	120/78	96	120/80	92	-
M. B.	20	120/68	80	148/82	64	9

SUMMARY AND CONCLUSIONS

Benzedrine, paredrine, and propadrine have marked and rapid blood-pressure-raising effects when given intravenously. Paredrine is the most effective. Propadrine is less effective than benzedrine, doses of 50 mg. of the former drug being approximately comparable to 20 mg. of the latter. With none of the three drugs is there any disturbance in cardiac rhythm. Slowing in pulse rate usually occurs with the increase in blood pressure.

For clinical use in conditions in which rapid and prolonged blood-pressure-raising effects are indicated, any of the three amines may be chosen. The doses recommended are: for benzedrine, 20 to 30 mg.; for paredrine, 10 to 15 mg.; and for propadrine, 50 mg. Since benzedrine has a central stimulating effect, paredrine and propadrine may be preferable in certain instances.

REFERENCES

1. Alles, G. A.: The Comparative Physiological Actions of dl-Beta-phenylisopropylamines. I. Pressor Effects and Toxicity, *J. Pharmacol. & Exper. Therap.* 47: 339, 1933.
2. Abbott, W. O., and Henry, C. M.: Paredrine (Beta-4 Hydroxyphenylisopropylamine) a Clinical Investigation of a Sympathomimetic Drug, *Am. J. M. Sc.* 193: 661, 1937.
3. Black, J. H.: The Control of Allergic Manifestations by Phenyl-Propanol-Amine (propadrin) Hydrochloride, *Journal-Lancet* 57: 101, 1937.
4. Boyer, W. E.: The Clinical Use of Phenyl-Propanol-Amine Hydrochloride (Propadrine) in the Treatment of Allergic Conditions, *J. Allergy* 9: 509, 1938.
5. Chen, K. K., Wu, C. K., and Henriksen, E.: Relationship Between the Pharmacological Action and the Chemical Constitution and the Configuration of the Optical Isomers of Ephedrine and Related Compounds, *J. Pharmacol. & Exper. Therap.* 36: 363, 1929.
6. Myerson, A., Loman, J., Rinkel, M., and Lesses, M. F.: The Effect of Amphetamine Sulfate (Benzedrine Sulfate) and Paredrine Hydrobromide Upon Sodium Amytal Narcosis. (To be published.)
7. Reifenstein, E. C., Jr., and Davidoff, E.: Intravenous Benzedrine Sulfate as an Antagonist to Intravenous Soluble Amytal, *Proc. Soc. Exper. Biol. & Med.* 38: 181, 1938.

A NEW PRECORDIAL ELECTRODE

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WITH the advent of the precordial electrode, many physicians have felt that the use of the ordinary type of silver electrode necessitated having the patient, or someone else, hold the electrode in place. As this is not always convenient, a precordial lead was devised with a suction cup to hold the electrode in place.† This simple device consists of a cup made of plastic material, through which an electrode of German

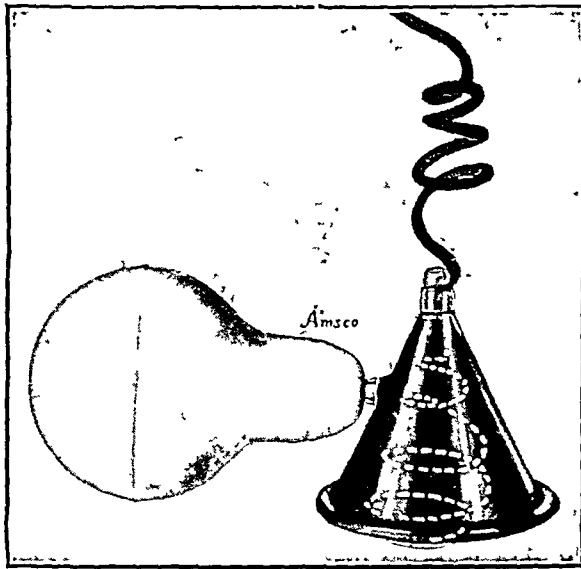


Fig. 1.

silver wire protrudes. Attached to this cup is a rubber bulb which is used to create suction sufficient to hold the electrode on the precordium, thus obviating the need of a nurse or the cooperation of the patient.

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†Manufactured by the American Medical Specialties Co., Inc., 131 East 23rd Street, New York, N. Y.

Received for publication Dec. 31, 1938.

Special Article

STANDARDIZATION OF BLOOD PRESSURE READINGS

JOINT RECOMMENDATIONS OF THE AMERICAN HEART ASSOCIATION AND THE
CARDIAC SOCIETY OF GREAT BRITAIN AND IRELAND

INTRODUCTION

IT HAS long been realized by thoughtful teachers and practitioners of medicine that the wide variations noted in blood pressure* records of the same individual were due not only to changes in the pressure from time to time under different conditions, but also to differences in the methods and interpretations used by the observers. A recent survey† revealed a serious lack of agreement among physicians as to the correct technique for measuring the blood pressure and interpreting the results obtained. Equally confusing was the situation among insurance companies as to what they should require of their examiners in this regard. Experiments with multi-aural stethoscopes demonstrated that recent years have brought little, if any, improvement in this situation, since the disagreement among the recently qualified was as great as that among attending physicians, and the range of error was too large among all groups tested. The Committees for the standardization of methods of making blood pressure readings appointed by the American Heart Association and by the Cardiac Society of Great Britain and Ireland have attempted to secure a crystallization of the best available thought on this subject.

The joint committees were asked, if feasible, to make recommendations which might be accepted as constituting standards for practicing physicians, medical teachers, insurance carriers, and all others interested in this problem. After a careful study of material available from many sources, the Committees of the American Heart Association and of the Cardiac Society of Great Britain and Ireland jointly recommend the following procedure as the standard method for taking and recording blood pressure readings in man.

STANDARDIZATION OF BLOOD PRESSURE DETERMINATIONS

Recommendations of the Committees for the Standardization of Blood Pressure Determinations

1. *Blood Pressure Equipment.*—The blood pressure equipment to be used, whether mercurial or aneroid, should be in good condition and

The recommendations contained in this report have been approved by the Association of Life Insurance Medical Directors of America.

*"Blood pressure," by common usage, signifies arterial pressure, and for that reason is so used throughout this report.

†Wright, I. S., Schneider, R. F., and Ungerleider, H.: Factors of Error in Blood Pressure Readings. AM. HEART JOUR. 16: 469, 1938.

calibrated at yearly intervals—more often if defects are suspected. (Mercurial preferred—British Committee.)

2. *The Patient*.—The patient should be comfortably seated (or lying—British Committee), with the arms slightly flexed and the whole forearm supported at heart level on a smooth surface. If readings are taken in any other position, a notation of that fact should be made. The patient should be allowed time to recover from any recent exercise or excitement. There should be no constriction of the arm by clothes, etc.

3. *Position and Method of Application of the Cuff*.—A standard-sized cuff containing a rubber bag 12 to 13 cm. in width should be used. A completely deflated cuff should be applied snugly and evenly around the arm with the lower edge about 1 inch above the antecubital space and with the rubber bag applied over the inner aspect of the arm. The cuff should be of such a type and applied in such a manner that inflation causes neither bulging nor displacement.

4. *Significance of Palpatory and Auscultatory Levels*.—In all cases palpation should be used as a check on auscultatory readings. The pressure in the cuff should be quickly increased in steps of 10 mm. Hg until the radial pulse disappears, and then allowed to fall rapidly. If the radial pulse returns at a higher level than that at which the first sound is heard, the palpatory reading should be accepted as the systolic pressure; otherwise the auscultatory reading should be accepted.

5. *Position and Method of Application of Stethoscope*.—The stethoscope should be placed over the previously palpated brachial artery in the antecubital space, not in contact with the cuff. No opening should exist between the lip of the stethoscope and the skin; this should be accomplished with the minimum pressure possible. The hand may be pronated or supinated, depending on which position yields the clearest brachial pulse sounds.

6. *Determination of the Systolic Pressure*.—The cuff should be rapidly inflated to a pressure about 30 mm. above the level at which the radial pulse can be palpated. The cuff should then be deflated at a rate of 2 to 3 mm. Hg per second. The level at which the first sound regularly appears should be considered the systolic pressure, unless, as pointed out above, the palpatory level is higher, in which event the palpatory level should be accepted. This should be noted.

7. *Determination of the Diastolic Pressure and the Pulse Pressure*.—With continued deflation of the cuff, the point at which the sounds suddenly become dull and muffled should be known as the diastolic pressure. If there is a difference between that point and the level at which the sounds completely disappear, the American Committee recommends that the latter reading should be regarded also as the diastolic pressure. This should then be recorded in the following form: RT* (or LT†) 140/80-70,

*RT = right arm.

†LT = left arm.

or 140/70-0. If these two levels are identical the blood pressure should be recorded as follows: 140/70-70. The cuff should be completely deflated before any further determinations are made.

The British Committee believes that except in aortic regurgitation it is nearly always possible to decide the point at which the change comes, and that this is the only reading which should be recorded.

EXPLANATORY COMMENTS

In addition to the above specific recommendations, the Committees believe that certain other factors should be taken into consideration by the physician who makes blood pressure determinations.

The relative merits of various types of sphygmomanometers have been the subject of numerous reports. In the opinion of the joint Committees, mercurial and aneroid types of apparatus are capable of correct readings if they are in good condition, and both types of equipment may produce inaccurate findings if not in good condition. This factor is often overlooked in the case of the mercury manometer, which should be checked at intervals as to the following points:

1. The level of the mercury at rest should be exactly at the zero mark. If some of the mercury has leaked out this will not be the case. The missing mercury should be replaced.

2. If the small air vent at the top of the glass tubing becomes clogged, a definite lag may be produced; the mercury column may not register the pressure in the bag, and the readings will therefore be incorrect.

3. The apparatus must be on a level surface, since tilting of the manometer will result in incorrect readings. It should also be level with the observer's eyes.

A yearly calibration of the aneroid type of instrument against a U-tube standard is recommended. This is particularly advisable for the older instruments, in which a sharp blow or fall may cause inaccuracies due to resultant changes in the aneroid diaphragm. The needle should stand at zero when the apparatus is completely deflated and move immediately when the inflation begins. Manometers which have a stop pin at zero, or those which have a rotatable dial, permitting the user to set the zero mark anywhere, are not recommended, since a satisfactory check with instruments of this type is impossible.

In both types of equipment the valves of the instrument, including those of the rubber bulb, should be competent and function smoothly. The entire system, including the "pressure" rubber tubing and rubber bag, must be free from leakage and must be kept in good condition. It is recommended that the instrument to be used be checked at yearly intervals against a machine known to be in perfect condition. More frequent checks should be made if the accuracy of the instrument is in doubt. The rubber cuffs should be 12 to 13 cm. wide and 23 cm. long.

The cloth covering should be of inextensible material of such a nature that even pressure is exerted throughout the width of the cuff; it should extend as a band 15 cm. wide for 60 cm. beyond the edge of the rubber cuff, and then taper gradually for an additional 30 cm. New types of cuff, using a "zipper" mechanism or hooks on a rib extending the width of the cuff, appeared to be more satisfactory than the long, tapering cuff end. If bulging occurs above and below the band the reading may not be accurate.

A special cuff should be used to measure blood pressure in the leg. The rubber bag should be 15 cm. wide, and its covering 17 cm. wide and 30 cm. longer than in the case of the armlet (total 120 cm.). For children, cuffs of the following widths have been suggested: under eight years, less than 9 cm.; under four years, less than 6 cm.; newborn babies, less than 2½ cm. The limited work done in this field does not warrant a definite recommendation at this time.

The American Committee selected the sitting position as the preferable one because of the fact that it simplifies the taking of large numbers of blood pressure readings. It is true that many patients are bedridden, but in most instances they may be propped up into a sitting position without causing more than transitory disturbances in the circulation; and when this is impossible it is suggested that a notation be made as to the position in which the blood pressure is taken. The British Committee did not think that there was any significant difference between the sitting and lying positions. For blood pressure readings in the thighs, the stethoscope bell should be placed over the popliteal artery with the patient prone.

Certain physical and psychologic factors should be considered. Inquiry should be made as to the patient's activity just before the examination. Exercise and meals affect the blood pressure. A rest period of from 10 to 15 minutes prior to the making of the observations will eliminate or minimize certain of these factors. It is important that the physician evaluate the degree of stress or emotional crises through which the patient may be passing. The first reading taken by a physician is often much higher than later ones, due to apprehension and nervousness on the part of the patient. It is often wise, therefore, to avoid conclusions regarding the blood pressure level of an individual until several readings have been made on successive visits. This is especially important with hypertensive and hyperthyroid patients. Any evidence of apprehension or of undue concern on the part of the physician may alarm the patient and increase the pressure.

There are variations in the blood pressure level of certain individuals in the course of a day. It is therefore suggested that for careful records the time of the day should be noted, and if the patient is being carefully followed with reference to the blood pressure level the observations

should be made at essentially the same time and in the same relationship to meals, sleep, exercise, and other similar factors.

The term "points" is suggested for use in reference to diastolic pressure, since the word "phase," formerly used, implies a measure of time interval, whereas in reality the fourth and fifth "points" are the exact levels at which change is made from one phase to the next. Detailed discussion of the second and third phases is not pertinent to this report, since those phases are of little, if any, practical importance and tend to confuse the issue at hand. It should be clearly recognized that a single figure for systolic or diastolic pressure apparently does not represent actual pressure within from 5 to 10 mm. of mercury. If the physician wishes to minimize the sources of error several blood pressure readings should be made, the highest and lowest being recorded. Although an average of the series of readings might be recorded, this would not have the same significance in instances of cardiac irregularity.

The determination of blood pressure in arrhythmias is unsatisfactory, at best, when made with the apparatus under discussion. With premature beats the higher systolic pressure of the beats that terminate compensatory pauses should be ignored. With auricular fibrillation both diastolic and systolic readings should be recorded as approximate only. It is suggested that in this condition the average of a series of readings for the appearance of the first sound be noted as the systolic pressure, and that similar averages for the fourth and fifth "points" be recorded as the diastolic pressure. The diagnosis, if not stated elsewhere on the patient's chart, should be noted with the blood pressure recording. In aortic regurgitation with a collapsing pulse the diastolic end point is sometimes marked by a less obvious change in the quality of the sounds than normally. This change may be difficult to appreciate.

Alternation of the pulse during blood pressure determinations may indicate left ventricular weakness.

It is suggested that, when especially careful studies of the blood pressure are to be made, the use of basal blood pressure conditions should be considered. A preparation similar to that used prior to measuring the basal metabolic rate is recommended. Such a basal blood pressure determination should be made 10 to 12 hours after a meal (preferably in the morning), after the patient has rested for 30 minutes in a comfortably warm room. The patient should be mentally, as well as physically, at ease. This procedure would be most useful in experimental studies in which an accurate standard level is desired. Objections to its use in general practice are obvious.

When auscultatory methods alone are used, the actual blood pressure level may be definitely higher than the level at which the first sounds are detected. Under these circumstances, the palpatory reading will be the more nearly correct of the two. If both palpatory and auscultatory methods are used, as recommended, this error will be detected.

In occasional instances, the usual sounds are heard over the brachial artery at a fairly high level; as the pressure in the cuff is reduced, the sounds completely disappear, only to reappear at a distinctly lower level. This zone of silence is known as the auscultatory gap. Its existence is obviously important, inasmuch as it is possible in such patients to inflate the cuff only to the level of the auscultatory gap, and to record the systolic pressure at the level where sounds are first heard, which may actually be 40 or 50 mm. below the true systolic level.

The importance of avoiding unnecessary venous congestion should be recognized. This can be minimized by making certain that there are no constricting bands on the patient's arm, and that the pressure cuff is not kept inflated longer than absolutely necessary to make the blood pressure reading. Decompression should be at the rate of approximately 2 to 3 mm. Hg per second. After making a reading, the cuff pressure should be reduced to zero long enough to allow the veins to empty before another determination is started.

It is suggested that on the first examination of the patient the blood pressure be taken in both arms, since the two may not be the same. If the patient is followed for a period of time this procedure might wisely be repeated at stated intervals of every few months, and at other times if indicated by developments. In the presence of unexplained high pressure in the brachial arteries it is suggested that the blood pressure in the legs be taken also. By this procedure conditions such as coarctation of the aorta may be detected.

If the variations in blood pressure which occur with respiration are considerable, this factor may be eliminated by taking a reading while the patient holds his breath at midrespiration, but this must be for only a short interval, or abnormal blood pressure readings, due to asphyxia and other factors, will result.

Certain factors inherent in the physician, such as variations in accuracy of hearing, must be recognized as important. A physician who is aware that his hearing has become impaired should use a stethoscope in which sound is amplified to a considerable extent, and in the event of marked deafness electrically amplified or other mechanical devices should be utilized. It is thought inadvisable at this time to make recommendations regarding automatically recording blood pressure equipment.

The combined use of the auscultatory and palpatory methods, as described herein, will yield routine data that are as reliable as those given by any other method. Under exceptional circumstances, as when the pulse is too feeble to produce sounds or too irregular for averaging, recording methods may become necessary. Those contemplating the use of graphic methods should first ascertain through reliable sources whether they will subserve the ends in mind.

The recommendation of a standard procedure, as outlined by the Committees, is not intended to discourage initiative when indicated in special situations.

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AURICULAR FIBRILLATION OF TWENTY-TWO MONTHS' DURATION, WITH RETURN TO NORMAL SINUS MECHANISM WITHOUT THE AID OF QUINIDINE

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SEARCH of the literature failed to reveal a report of a single case of auricular fibrillation of long duration in which reversion to normal sinus mechanism occurred without the use of quinidine or related drugs. Bishop¹ reports four patients whose auricular fibrillation was supplanted by normal sinus mechanism without the aid of specific therapy. In two of the patients electrocardiograms are presented which demonstrate the existence of auricular fibrillation and normal sinus mechanism. The abnormal and normal mechanisms were recorded at approximately two- and three-year intervals, respectively. In neither instance, however, is it stated whether or not the fibrillation was continuous throughout this time. The histories would suggest that both patients might have been suffering from paroxysms of fibrillation. Again, there is no indication that either patient was seen at frequent intervals, so that possible changes in rhythm could have been detected.

Paroxysmal auricular fibrillation of short duration, especially in patients with hyperthyroidism, is well known.^{2, 3, 4} Again, auricular fibrillation of long duration, fifteen years, or more, without return to normal mechanism, has been reported.^{2, 5} Kohn and Levine⁶ described twenty patients with auricular fibrillation of over one year's duration. With the aid of quinidine fifteen of these regained normal sinus mechanism. Similar experiences have been reported by others.^{7, 8} However, the patient to be described is unique in that he had had auricular fibrillation (verified by electrocardiograms) continuously for 22 months, at the end of which time normal sinus mechanism returned without the aid of quinidine or related drugs.

CASE REPORT

M. S., a white man, 61 years of age, entered the Outpatient Department of Charity Hospital May 18, 1935, complaining of dyspnea, edema of the feet, weakness, and palpitation. The patient had been suffering from mild dyspnea on marked exertion for several weeks, but with sudden muscular exertion the day before enter-

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Received for publication Dec. 9, 1938.

ing the clinic he suddenly experienced palpitation, faintness, and extreme dyspnea. On admission to the clinic, the patient's palpitation and dyspnea had decreased, but edema had developed progressively in the legs and feet. On examination the patient was found to have an absolute irregularity of his pulse, generalized senile arteriosclerosis, a heart rate of 108 per minute, and a blood pressure of approximately 180/110.

The heart was enlarged, and there was a soft, blowing, systolic, mitral murmur. There were fine moist râles in the bases of both lungs. The liver was enlarged, and there was edema of both legs and feet. The blood Wassermann reaction was found to be strongly positive. An electrocardiogram showed auricular fibrillation (Fig. 1), and a teleoroentgenogram showed that the heart was enlarged; the transverse diameter of the heart was 17.8 cm., the transverse diameter of the thorax 31 cm., and the longitudinal diameter of the heart 17.6 cm. Other laboratory studies failed to show anything significant.

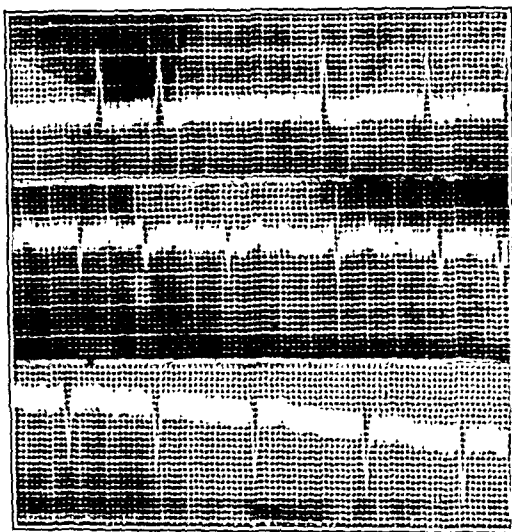


Fig. 1.—Electrocardiogram showing auricular fibrillation, taken May 18, 1935.

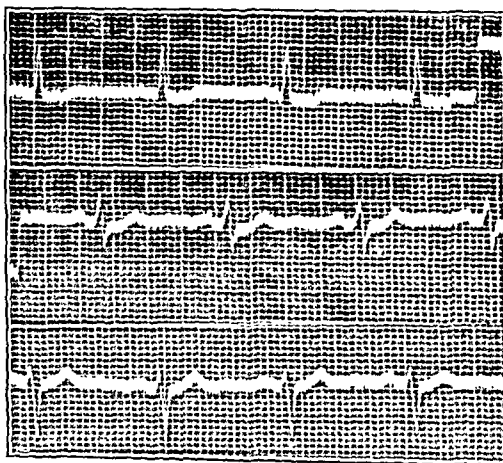


Fig. 2.—Electrocardiogram showing normal sinus mechanism, taken March 26, 1937.

The patient was digitalized. Twenty-five drops of the standard tincture, three times daily, were found necessary for maintenance. Since the patient was suffering

from rather severe congestive heart failure, but would not be admitted to the hospital and, therefore, could be seen only at relatively long intervals, quinidine was not administered. Antisyphilitic treatment was started. Arsenical preparations were not employed until he had received mild antisyphilitics for many months.

Progress.—The patient was seen at weekly intervals for a few months, and every two weeks thereafter. He responded rapidly to treatment, but his auricular fibrillation continued. The ventricular rate was reduced to 70-80 per minute. A few weeks after digitalization was established, 30 drops of standard tincture of digitalis, three times daily, were found necessary for maintenance.

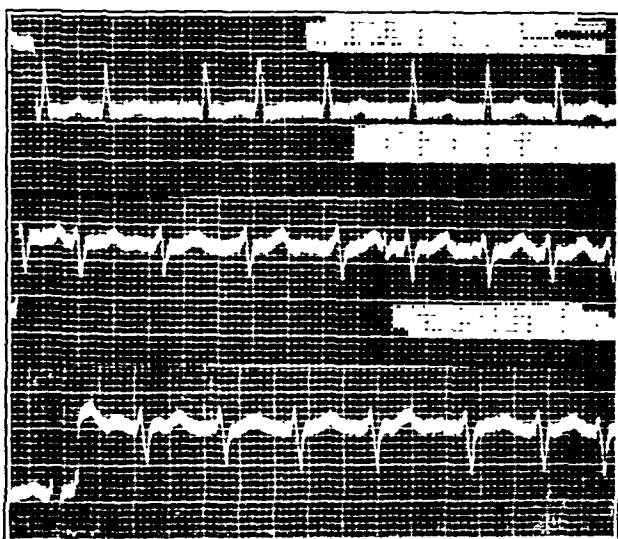


Fig. 3.—Electrocardiogram showing auricular fibrillation, taken Jan. 5, 1938.

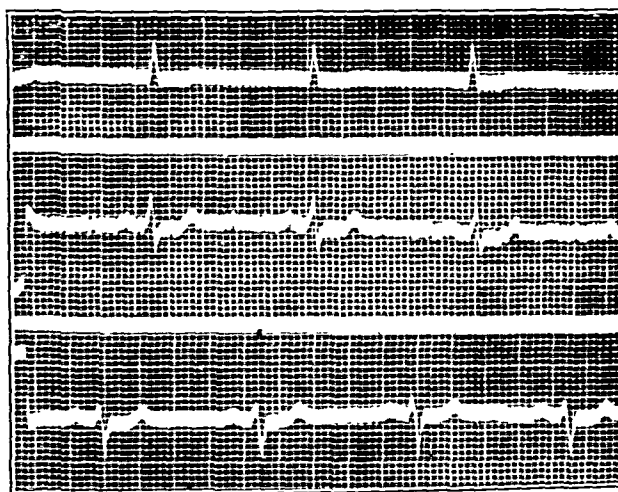


Fig. 4.—Electrocardiogram showing normal sinus mechanism, taken Sept. 14, 1938.

The electrocardiogram, from time to time, showed no definite differences from the original, except that the ventricular rate had been slowed. On March 26, 1937, the patient's radial pulse and heartbeat were found to be regular. All previous evidences of auricular fibrillation had disappeared. An electrocardiogram revealed normal sinus mechanism (Fig. 2). The cardiac mechanism remained normal until Jan. 5, 1938, when clinical evidence of auricular fibrillation reappeared, and its presence was verified by an electrocardiogram (Fig. 3). On Feb. 3, 1938, the blood

Wassermann reaction was found to be negative, and has remained so since. The patient's state remained uneventful until Sept. 14, 1938, when his pulse and heart-beat again became regular and slow, and his blood pressure dropped to 110/60. The patient's blood pressure previously had never been below 160/100. The blood pressure measurements were only approximate during the periods of fibrillation. An electrocardiogram at this time showed normal sinus mechanism (Fig. 4), and in the teleroentgenogram the cardiac measurements were as follows: transverse diameter of the heart, 11 cm.; longitudinal diameter of the heart, 13 cm.; diameter of the great vessels, 8 cm., and transverse diameter of the thorax, 32 cm. The patient was instructed to reduce the dose of his digitalis to 25 drops, three times daily. Another electrocardiogram, made on Sept. 21, 1938, showed frequent premature ventricular contractions. However, one week later these premature contractions had disappeared and normal sinus mechanism persisted.

For forty weeks the patient received continuous antisypilitic treatment, consisting of courses of mercury rubs, potassium iodide, and 55 intramuscular injections of bismuth preparations and 59 of bismarsen, the latter being given during the final weeks of his treatment.

COMMENT

This patient was definitely known to have had auricular fibrillation for twenty-two months. The diagnosis was sustained by electrocardiograms taken May 18, 1935, when the patient was first seen, and at frequent intervals until March 26, 1937, when normal sinus mechanism was detected. It would be impossible to determine the length of time the patient had suffered from auricular fibrillation prior to his first visit to the Charity Hospital Outpatient Clinic, as he had not seen a physician for a number of years previous to the onset of his present illness. His history would suggest, however, that the auricular fibrillation probably began the day before he entered the medical clinic, when sudden physical exertion precipitated the acute attack of dyspnea and palpitation. The latter symptom persisted; it was the first such attack the patient had ever experienced.

Many factors have been alleged to favor the persistence of auricular fibrillation, viz., focal infections, general diseases, local strain of muscles or joints, painful conditions, like stones in the kidneys or gall bladder, and heart failure.⁵ There appears to be no relationship between the syphilitic infection and the behavior of the abnormal cardiac mechanism. Auricular fibrillation is known to be rare in syphilitic heart disease. Furthermore, there was no clinical evidence that syphilis was an active etiologic factor in producing the heart disease. The systemic syphilitic infection, acting as a "general disease," might possibly favor the persistence of auricular fibrillation, but this is not likely, as the auricular fibrillation had ceased for a period of nine months and had returned again before the blood Wassermann reaction became negative. It is extremely doubtful whether the syphilitic infection played a significant role in influencing the behavior of the cardiac mechanism.

Congestive heart failure might influence the duration of auricular fibrillation, but this was apparently not a factor in our case, for the patient's heart failure had completely disappeared many months before normal sinus mechanism returned. Furthermore, the cardiac mechanism changed from auricular fibrillation to normal sinus mechanism, back to fibrillation, and again to normal sinus mechanism, without any evidence that the patient had congestive heart failure.

Digitalis has been reported to restore normal mechanism when administered in large single doses shortly after the onset of the auricular fibrillation.⁹ On the other hand, the drug has also been said to bring on auricular fibrillation.¹⁰ It is quite unlikely that the digitalis administered to this patient influenced the auricular fibrillation, except by slowing the ventricular rate, for the abnormal mechanism started before the patient had received any digitalis, and the cardiac mechanism reverted to normal, then to fibrillation, and back to normal, while he was still under the influence of digitalis. Therefore, it cannot safely be said that the reversion of the cardiac mechanism to normal was related to digitalis.

The decrease in cardiac size is of interest. In spite of the many months of auricular fibrillation, the cardiac size decreased from a state of definite enlargement to within the limits of normal. Auricular fibrillation might produce slight cardiac enlargement,⁵ but it is doubtful whether it would favor its disappearance. The observations of Stewart, et al.,¹¹ show that digitalis will decrease the cardiac size in patients with auricular fibrillation and congestive failure. Whether this factor alone is sufficient to explain the pronounced decrease in cardiac size in this patient can only be conjectured, although it was probably one of the contributing factors. The reduction in cardiac size probably indicates, also, a decrease in cardiac strain, or a repair of an abnormal myocardial state independent of the strain, or both. The mechanism of the decrease in cardiac size remains obscure, as well as its relationship to the abnormal cardiac mechanism.

A satisfactory explanation for the behavior of the cardiac mechanism cannot be advanced at the present time. The patient will continue under observation, during which time etiologic factors responsible for the arrhythmia will be sought.

SUMMARY

The case of a patient with definite auricular fibrillation of 22 months' duration, in which cardiac mechanism returned to normal without the aid of quinidine or related drugs, is presented. Apparently, no such case has been reported previously. Factors possibly influencing the disturbed cardiac mechanism are discussed.

REFERENCES

1. Bishop, L. F.: Fibrillation of the Auricle Returned to Normal Rhythm, *Am. J. M. Sc.* 165: 29, 1923.
2. Evans, W. A.: Long-Standing Cases of Auricular Fibrillation With Organic Heart Disease; Some Clinical Considerations, *Ann. Int. Med.* 9: 1171, 1936.
3. Williams, F. A.: Auricular Fibrillation and Life Expectancy, *Minnesota Med.* 3: 365, 1920.
4. Phillips, J., and Anderson, J. P.: Cardiac Disturbances in Goiter, *J. A. M. A.* 89: 1380, 1927.
5. White, P. D.: Heart Disease, Ed. 2, New York, 1937, The Macmillan Company.
6. Kohn, C. M., and Levine, S. A.: An Evaluation of the Use of Quinidine Sulfate in Persistent Auricular Fibrillation, *Ann. Int. Med.* 8: 923, 1935.
7. Orgain, E. S., Wolff, L., and White, P. D.: Uncomplicated Auricular Fibrillation With Auricular Flutter, *Arch. Int. Med.* 57: 493, 1936.
8. Viko, L. E., Marvin, H. M., and White, P. D.: A Clinical Report on the Use of Quinidine Sulphate, *Arch. Int. Med.* 31: 345, 1923.
9. Schwartz, S.: The Effects of Digitalis on Premature Auricular Contractions Associated With Attacks of Paroxysmal Auricular Fibrillation. The Use of the Drug in the Treatment and Prevention of Certain Forms of These Arrhythmias, *AM. HEART J.* 6: 458, 1930-31.
10. McEachern, D., and Baker, B. M., Jr.: Auricular Fibrillation; Its Etiology, Age Incidence and Production by Digitalis Therapy, *Am. J. M. Sc.*, 183: 35, 1932.
11. Stewart, H. J., Deitrick, J. E., Crane, N. F., and Wheeler, C. H.: Action of Digitalis in Uncompensated Heart Disease, *Arch. Int. Med.* 62: 569, 1938.

COMPLETE TRANSPOSITION OF THE AORTA AND PULMONARY ARTERY

IN ONE CASE, WITH PATENT DUCTUS ARTERIOSUS AND FORAMEN OVALE,
AND, IN ANOTHER, WITH INTERVENTRICULAR SEPTAL DEFECT
AND PULMONIC STENOSIS

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BOSTON, MASS.

IN HER analysis of 1000 cases of congenital heart disease, Maude Abbott¹ found only thirty-eight cases of complete transposition of the great vessels associated with patency of the ductus arteriosus and foramen ovale. The association of complete transposition with interventricular defect occurred in thirty-six cases, only seventeen of which were analyzed. Because of the comparative rarity of this lesion, two additional cases are here reported.

CASE 1.—Baby Boy D, 3 weeks old, only child of normal white parents, was born Dec. 3, 1937, after an easy breech delivery, and was transferred from the nursery to the children's ward on Dec. 27, 1937. He showed cyanosis and labored breathing from birth, at which time there was considerable mucus in the respiratory tract. Physical examination revealed a well-nourished, well-developed male infant, appearing very cyanotic and dyspneic. The blueness was generalized, more marked in the circumoral and nasal regions and less in the fingers and toes, and became less intense after crying. The cry was strong, the muscle tone good, and the baby was active and responsive. There was a soft systolic murmur at the mitral area, transmitted to the axilla and up the sternum. This murmur was discovered Dec. 7, 1937, at which time it was heard over the entire precordium, loudest under the sternum at the second intercostal space. The spleen was palpable two fingerbreadths below the costal margin. The temperature varied between 99° and 100° F.; the pulse rate was about 90 until the last few days, when it rose to 140-150.

Laboratory Findings

Dec. 6, 1937

Erythrocyte count,	3,500,000
Hemoglobin,	85 per cent
Leucocyte count,	20,150
Neutrophils,	65 per cent
Lymphocytes	34 per cent
Monocytes	1 per cent

Dec. 28, 1937

Erythrocyte count,	3,710,000
Hemoglobin,	65 per cent
Leucocyte count,	11,950
Neutrophils,	25 per cent
Lymphocytes	73 per cent
Monocytes	2 per cent

From the Department of Roentgenology and Pathology of the New England Hospital for Women and Children.

Received for publication Dec. 9, 1938.

The urine was normal. The mother had a negative Hinton test. The electrocardiogram was interpreted as follows:² "Normal rhythm at a rate of 170. The P waves are of short duration and sharply peaked in Leads II and III. The P-R interval is 0.1 second. The QRS complexes are normal in duration and amplitude, but there is marked right axis deviation. The S-T segments are slightly elevated in all leads. The T waves are normal and upright in Leads I and II and slightly inverted in Lead III. Lead IV is normal. This electrocardiogram is consistent with the diagnosis of congenital heart disease."

Roentgenologic study a few hours after birth revealed no enlargement of the cardiac shadow as a whole, though the elevation of the apex suggested hypertrophy of the right ventricle (Fig. 1). The lungs appeared incompletely aerated. A repeat examination, with fluoroscopy, nine days later, however, showed a definite increase in the size of the heart (Fig. 2). The enlargement appeared to be due both to auricular dilatation and ventricular hypertrophy and dilatation. The appearance was that of congenital cardiopathy. The aortic shadow seemed small. The lesion suggested was patent ductus arteriosus.

After delivery the infant lived in an oxygen tent. Carbon dioxide was given at frequent intervals, as well as coramine and other respiratory stimulants. There was no difficulty in feeding until the terminal stage, beginning Dec. 28, 1937. The general condition became progressively worse, the respirations more labored, irregular, and slower. The cyanosis increased. There was no response to stimulation, and the baby died Jan. 1, 1938.

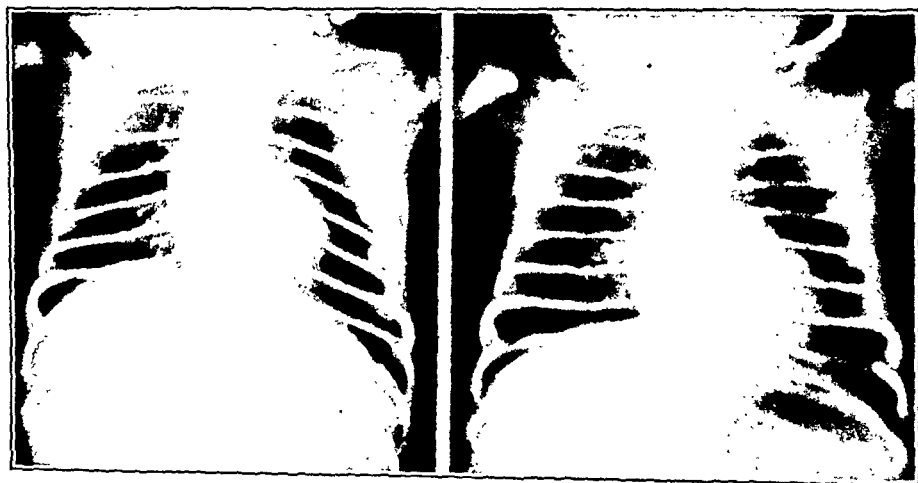


Fig. 1.

Fig. 2.

Fig. 1.—Case 1, Dec. 4, 1937. Note normal size of cardiac shadow and elevation of apex.

Fig. 2.—Case 1, Dec. 13, 1937. The heart has enlarged since the previous examination.

The post-mortem findings relative to the heart were as follows: The heart was large, measuring 6.5 cm. transversely. The thoracic cage at the same level measured 10 cm. The heart showed two ventricles and two auricles with pulmonary veins and venae cavae entering in the normal manner. The right ventricle was very large and relatively thick-walled. The aorta arose from the right ventricle, and the innominate, left subclavian, and left common carotid arteries arose in the usual manner from the aortic arch. The pulmonary artery arose from the left ventricle, and divided into right and left branches. The ductus arteriosus was widely patent. The foramen ovale was also patent. There was no ventricular defect. The valves were normal (Figs. 3, 4, 5).

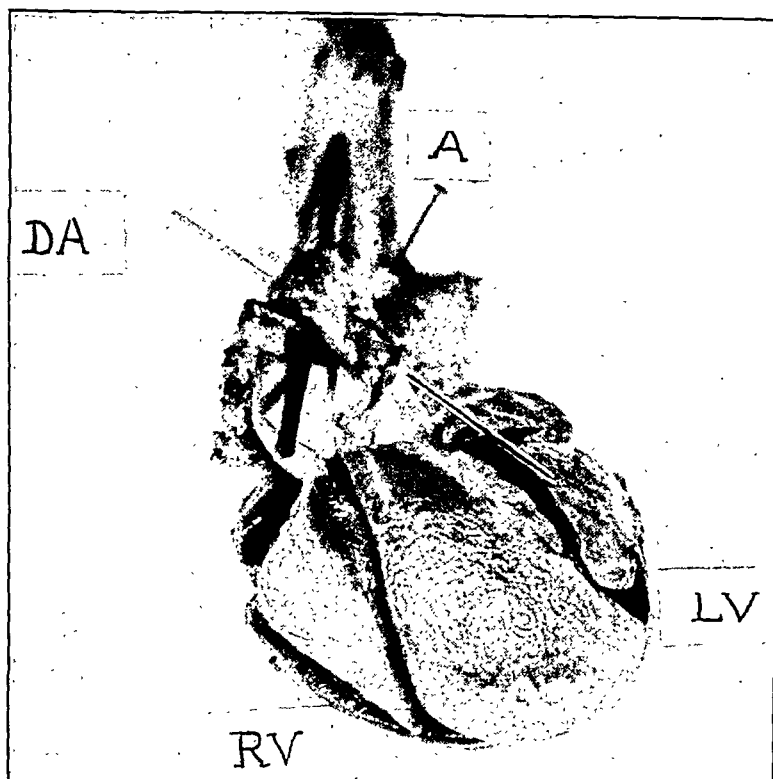


Fig. 3.—Case 1, DA—Ductus Arteriosus; A—Aorta; RV—Right Ventricle; LV—Left Ventricle. Dark probe extends through aortic valve into aorta; glass probe goes through ductus arteriosus.

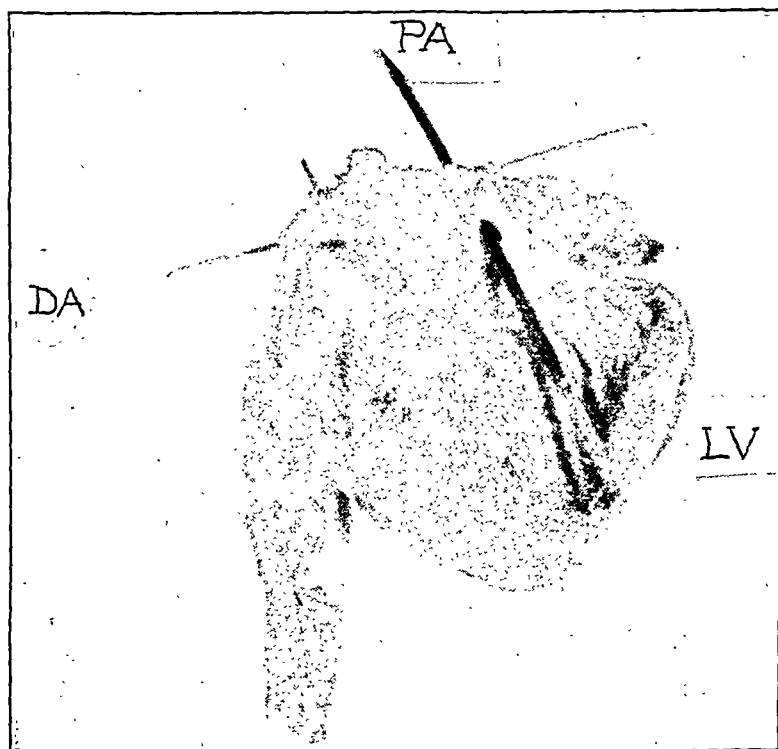


Fig. 4.—Case 1, PA—Pulmonary Artery; DA—Ductus Arteriosus; LV—Left Ventricle. Dark probe goes from left ventricle into pulmonary artery.

The heart weighed 55 gm. The wall of the left ventricle measured 4 mm., the wall of the right ventricle 5 mm., the mitral valve 3.5 cm., the aortic valve 2.4 cm., the pulmonary valve 2 cm., and the tricuspid valve 4.2 cm.

The complete pathologic diagnosis was: (1) Congenital anomaly of the heart, namely, transposition of the aorta and pulmonary arteries, patent ductus arteriosus, and patent foramen ovale; (2) extreme hyperemia, universal; (3) atelectasis of the lungs; and (4) hemorrhage into the lungs, intestines, and pancreas.



Fig. 5.—Case 1, Patent foramen ovale visualized.

CASE 2.—Baby Robert O, 8 weeks old, was readmitted to the children's ward Aug. 18, 1938, because of "stiffening of the limbs," a "queer cry," and cyanosis from birth. Delivery on June 21, 1938, was an easy left occipitoanterior with labor lasting five hours. The baby's color was dusky bluish. At that time examination revealed a loud systolic murmur all over the precordium. Because of vomiting after feeding, he was transferred to the children's ward July 5, 1938. With this regurgitation he had attacks of very rapid and irregular respiration (rate 24-38), with a pulse rate between 120 and 160. On discharge, July 24, 1938, he had gained 7 oz. in weight. There was no vomiting, but he was still blue, and his respirations were rapid and irregular. On re-entry there were marked cyanosis, tetanic spasm, a rapid pulse rate, and marked dyspnea. The cardiac murmur was not as distinct as before. The aortic second sound was louder than the pulmonic second. He was placed in an oxygen tent and given codeine and digitalis, but he rapidly became more cyanotic. He assumed an opisthotonos position. His respiratory rate increased (40-72), then the pulse and respirations slowed and ceased on Aug. 20, 1938.

Laboratory Findings

Hemoglobin,	70 per cent
Erythrocyte count,	4,780,000
Leucocyte count,	6,450
Neutrophils,	11 per cent
Large lymphocytes,	4 per cent
Small lymphocytes,	67 per cent
Monocytes,	14 per cent
Eosinophils,	3 per cent
Basophils,	7 per cent

The electrocardiogram showed² "normal rhythm at a rate of 160 a minute. The P waves are normal, but sharply peaked in Lead II, and the P-R interval is 0.13 second. The QRS complexes are normal in amplitude and duration, but their chief wave is downwardly directed in all leads. This results in an extreme degree of right axis deviation. The S T segments are slightly elevated in all leads. The T waves are upright and normal in all three leads."



Fig. 6.—Case 2 Note widened supracardiac shadow and enlargement to the right of the right auricle.

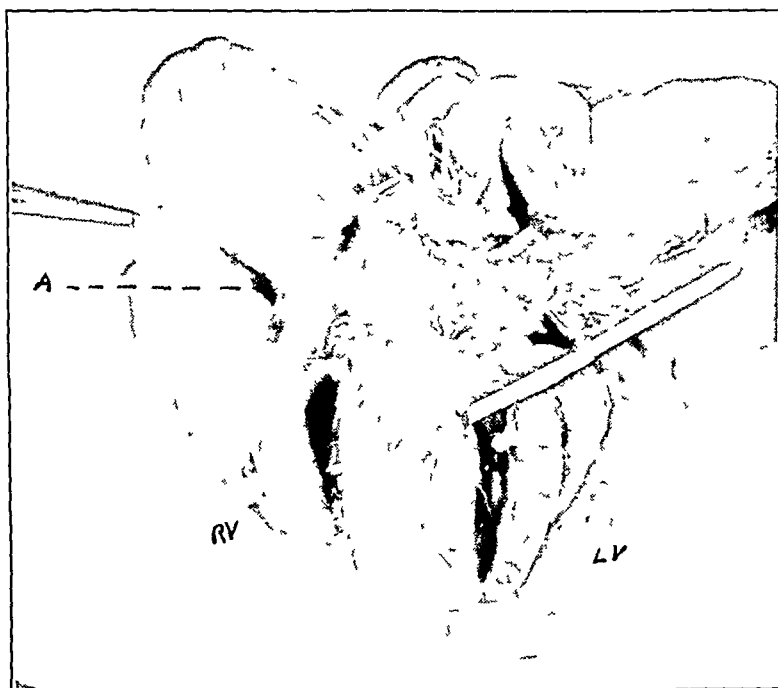


Fig. 7.—Case 2. A—Aorta, glass probe in ductus arteriosus, probe through interventricular septal defect

Roentgenologic study revealed no definite enlargement of the cardiac shadow. The supracardiac shadow was broadened and more prominent on the right side; there was also widening in the region of the right auricle (Fig. 6).

Post mortem examination revealed the following findings:

The thymus weighed 7 gm.; it was pink and soft, with moderately engorged vessels. The heart appeared very large; it measured 5 cm. transversely at the auriculoventricular junction; the right auricle was widely distended with blood and soft clot. The aorta arose from the right ventricle, measuring 1.3 cm. in diameter at ascending arch. The innominate, left common carotid, and left subclavian arteries arose normally from the arch. The ductus arteriosus was patent, but contained some firm clot. The pulmonary artery was relatively small, 8 mm. in diameter; it divided normally into right and left branches. The pulmonary valve had but two cusps. At the base of the pulmonary valve there was a small pouch-like structure, 5 mm. in diameter, beneath which there was a large, round opening, 7 mm. in diameter, between the ventricles. The foramen ovale was closed by a fenestrated membrane, leaving, however, an easily dilatable channel through which a probe was readily passed from right to left auricle.

The wall of the right ventricle measured 6-7 mm., that of the left ventricle 4 mm., the mitral valve 3 cm., the aortic valve 2.5 cm., the pulmonary valve 8 mm., and the tricuspid valve 4 cm. The right and left subclavian veins were much dilated.

Diagnosis.—Transposition of the great vessels; pulmonic stenosis; defect in the interventricular septum; early lobular pneumonia; universal passive congestion.

In the study of congenital heart disease the roentgenologic examination has not yet proved as exact a diagnostic procedure as it is for other cardiac lesions. For this reason, any case in which autopsy findings can be correlated with roentgenologic studies may lead to more accurate knowledge. In Case 1, the first examination showed an apparently normal cardiac outline. The second, nine days later, however, revealed enlargement in the transverse diameter and length. This enlargement was not globular; it was definitely more prominent on the left side. The measurements were as follows:

<i>Dec. 4, 1937</i>		<i>Dec. 31, 1937</i>	
Right median,	2.05 cm.	Right median,	2.4 cm.
Left median,	2.4	Left median,	3.5
Transverse,	4.45	Transverse,	5.9
Pulmonary field,	11.1	Pulmonary field,	11.1

The auricular shadows bulged into the posterior mediastinal space. The aortic shadow remained small. Post-mortem examination showed that the enlargement was due to hypertrophy and dilatation of the right ventricle, with dilatation of all other chambers. It is interesting to note that at birth the diagnosis of atelectasis was suggested because of the large amount of mucus in the trachea and the absence of physical signs of heart disease. Yet the cyanosis at that time was greater than is consistent with the degree of incomplete aeration revealed by the first roentgenogram. Later, both clinical and roentgenologic findings pointed to definite congenital cardiopathy. On the other hand, in Case 2 no cardiac enlargement was demonstrated, either roentgenologically or by physical examination. There is a possibility that the broadened supracardiac shadow represented the dilated subclavian veins and the trans-

posed blood vessels. The marked cyanosis, dyspnea, and loud systolic murmur made the diagnosis of congenital heart disease definite. In both of these patients an enlarged right ventricle was found at post mortem, yet the cardiac outlines were not similar and did not show the "coeur en sabot" contour that has been regarded as evidence of right ventricular enlargement.³

SUMMARY

This is a report of two cases of complete transposition of the great vessels, associated, in one case, with patency of the ductus arteriosus and foramen ovale, and in the other, with an interventricular septal defect and pulmonic stenosis. Both patients were studied clinically, roentgenologically, and by post-mortem examination.

REFERENCES

1. Abbott, Maude E.: Atlas of Congenital Heart Disease, The American Heart Association, New York, 1936.
2. Graybiel, Ashton: Personal Communication.
3. White, Paul D.: Heart Disease, Chapter 12, New York, 1937, Macmillan Company.

PAROXYSMAL BUNDLE BRANCH BLOCK CONVERTED INTO TWO-TO-ONE BUNDLE BRANCH BLOCK BY MEANS OF ATROPINE

CASE REPORT*

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CLEVELAND, OHIO

THE question whether or not the main branches of the His-Tawara bundle are subject to the influence of the vagus nerves is as yet unsettled. Drury and Mackenzie¹ were unable to demonstrate any effect on branch conduction, either by the use of acetylcholine or by stimulation of the vagi in the neck, in normal dogs. If, however, either the right or the left branch was injured mechanically, bundle branch block complexes appeared in the electrocardiogram for a short period of time, after which what appeared to be full recovery occurred. At a critical period following this recovery, bundle branch block complexes could be made to *reappear* by stimulation of the vagi in the neck. The authors attributed this effect to action of the vagus on the junctional tissues, rather than on the bundle branches. They thought that vagal stimulation increased the "decrement" through the A-V node and the main bundle, and consequently the impulse arrived at the still partially damaged branch too weak to pass, whereas it passed the undamaged branch readily.

This report deals with a patient, one of whose bundle branches was damaged but was still capable of fluctuation in conductivity.

CASE REPORT

Mrs. J. W., a 64-year-old white woman, entered the Evans Memorial Hospital complaining of weight loss, palpitation, and nervousness, of six months' duration. Aside from mild dyspnea on exertion and palpitation, there had been no significant cardiorespiratory symptoms. The past history was irrelevant. Physical examination revealed an adenomatous thyroid and signs of hyperthyroidism. The heart was not enlarged, and its action was rapid but regular. There was a precordial systolic murmur. The blood pressure was 170/95. There was moderate peripheral arteriosclerosis.

Laboratory Findings.—A roentgenogram of the chest showed compression of the trachea by the thyroid gland; the heart was normal in size and contour, the aorta long and tortuous; the lungs were clear. The urine was normal. Morphologically, the blood cells were normal. The blood Wassermann and Kahn reactions were negative. The vital capacity was 1500 c.c. The basal metabolic rate ranged from plus 30 per cent to plus 40 per cent on repeated determinations.

Electrocardiograms.—At the time of admission to the hospital the electrocardiogram was normal save for inversion of the T wave in Lead IV. The heart rate was

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Received for publication Dec. 16, 1938.

then 103 per minute. Two days later, another electrocardiogram showed complete left bundle branch block and rather frequent auricular ectopic beats. There were no clinical indications that the heart had suffered any injury during this interval.

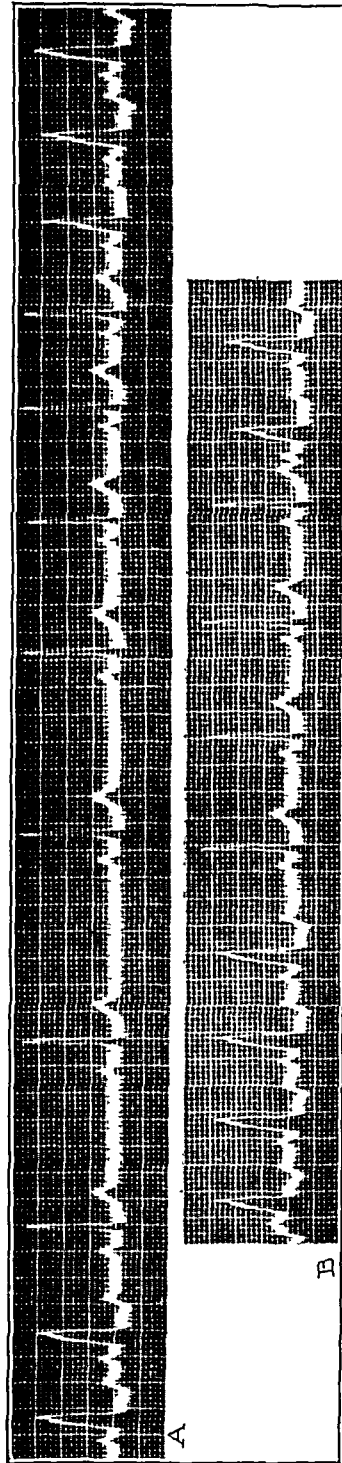


Fig. 1.—Lead I. Effect of vagal stimulation in neck on bundle branch block. A, Left carotid sinus pressure. Coincidental with slowing of the rate intraventricular conduction became normal. There is also prolongation of the P-R interval. B, Right carotid sinus pressure. Reduction in rate again brought about normal conduction.

The rate was somewhat faster, about 107 per minute. During the ensuing ten days electrocardiograms were repeated at frequent intervals, and, at times, they showed bundle branch block, while at other times there was normal conduction. Normal

conduction tended to be present at slow rates, and block at high rates of beating. While bundle branch block was present, observations were made on the effect of carotid sinus pressure and the administration of atropine intravenously. Fig. 1 shows the effect of carotid sinus pressure, and demonstrates the importance of a long diastolic pause in the recovery of conduction. This is further shown by Fig. 2, wherein two auricular ectopic beats occurred during a period of bundle branch block. The pause following one is only 0.02 second longer than that following the other. Fig. 3 *B* was taken four minutes after the intravenous injection of 3 mg. (gr. $\frac{1}{20}$) of atropine sulfate, and shows sinus tachycardia with 2:1 bundle branch block. This phenomenon persisted for eight minutes, when gradually the normal QRS complexes became transitional, then, finally, all complexes showed bundle branch block. During this time there was no significant variation of the blood pressure, and the full physiologic effect of the atropine was attested by dilation of the pupils and dryness of the mucous membranes.

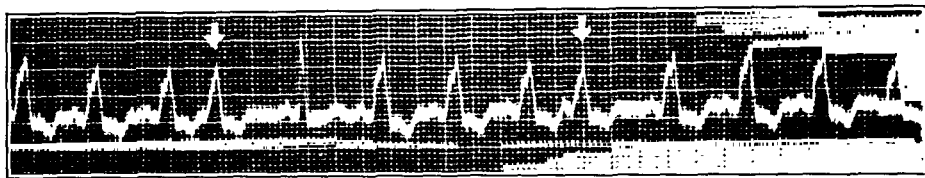


Fig. 2.—Lead I. Two auricular premature beats, illustrating the importance of a long diastolic pause as a factor in recovery of conduction. The pause preceding normal conduction measures 0.56 second, while that preceding the blocked impulse following the second premature beat measures 0.54 second.

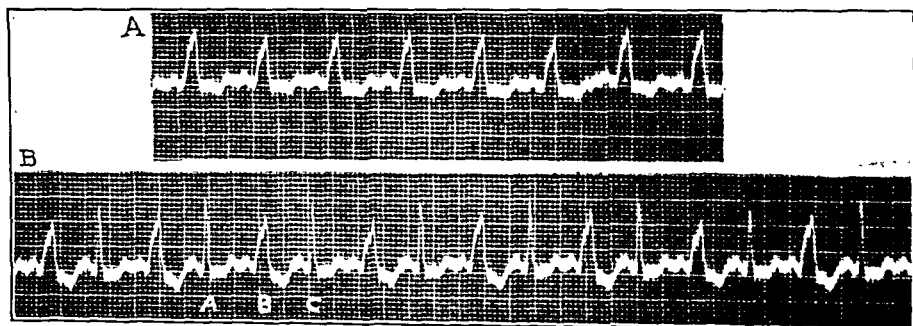


Fig. 3.—Lead I. Effect of atropine on bundle branch block. *A*, Taken immediately before injection. Rate about 100 per minute. *B*, Taken four minutes after the injection of 3 mg. of atropine sulfate intravenously. Rate about 140 per minute.

Following iodine therapy the pulse rate was persistently slower and the electrocardiograms persistently showed normal conduction, though bundle branch block could be made to reappear by accelerating the pulse by exercise.

The patient was transferred to the surgical service, and there underwent an uneventful thyroidectomy.

DISCUSSION

The subject of paroxysmal bundle branch block has recently been discussed by Comeau, Hamilton, and White,² and need detain us only long enough to emphasize the importance of a rapid rate of beating on the production of block in branches which are able to conduct normally if allowed a suitable recovery period.

Few reports of 2:1 bundle branch block with normal sinus rhythm have appeared in the literature; among them are the cases reported by Leinbach and White³ and Kelly.⁴

That stimulation of the vagus nerves can produce A-V block and that atropine can increase conductivity through A-V tissues is now well known, but whether this also holds for the bundle branches is certainly unsettled. We have already seen that normal conduction could be made to appear in this patient by sufficient lowering of the cardiac rate, and that as the time for recovery grew shorter with an increasing rate, conduction through the bundle became impaired. It is of some interest, therefore, to see that the administration of atropine can bring about normal conduction in alternate cycles in spite of a significantly increased heart rate.

The evidence for decremented conduction in the A-V tissue is not conclusive, so that it seems best not to suggest such an explanation, as Drury and Mackenzie did. It may well be that future observations will confirm the presence of decremented conduction and its control by vagal tone.

A second possible explanation involves a change in conductivity and refractory period in the bundle branches themselves. This explanation would be more impressive had the conduction become entirely normal, for it is readily apparent that the interval from *A* to *C* (Fig. 3) is well over that at which normal conduction occurred at slow rates. Hence no such mechanism need be invoked. Furthermore, this mechanism might be expected to affect both branches equally. Since the appearance of bundle branch block complexes does not necessarily imply complete block, but simply that the impulse arrives by way of the undamaged branch before it can pass the damaged one, any factor which affects conduction in both branches might be expected to leave the excitation of each ventricle and the form of the electrocardiogram unchanged.

A third, and perhaps the most likely explanation is that the mechanism is dependent on change of rate *per se*. It is apparent that during periods of block the impulse must have passed far enough into the damaged branch at each cycle to maintain some degree of refractoriness. If the rate is now sufficiently increased, impulse *B* (Fig. 3) will arrive during a period of high degree of refractoriness and may be completely blocked. Under these circumstances the recovery of the area is not interrupted, so that impulse *C* may then be able to pass. This, of course, is simply what is thought to occur in 2:1 A-V block, except that in that case no alternative pathway is open to the impulse.

CONCLUSION

A case of paroxysmal bundle branch block associated with hyperthyroidism is reported.

During a period of block the administration of atropine converted the mechanism into 2:1 bundle branch block.

The possible underlying mechanisms are discussed, and the conclusion reached that change in rate, quite apart from any local effect of atropine, may be sufficient to produce this phenomenon.

REFERENCES

1. Drury, A. H., and Mackenzie, D. W.: Aberrant Ventricular Beats in the Dog During Vagal Stimulation, *Quart. J. Exper. Physiol.* 24: 237, 1934.
2. Comeau, W. J., Hamilton, J. G. M., and White, P. D.: Paroxysmal Bundle Branch Block Associated With Heart Disease, *AM. HEART J.* 15: 276, 1938.
3. Leinbach, R. F., and White, P. D.: Two-to-One Right Bundle Branch Block, *AM. HEART J.* 3: 422, 1938.
4. Kelly, L. W.: Two-to-One Right Bundle Branch Block, *AM. HEART J.* 6: 285, 1930.

In Memoriam

JAMES WALLACE ESLER
1894-1938

PIONEER IN CARDIOLOGY IN WASHINGTON, D. C.

Many devoted patients and associates have been greatly saddened by the death, on Dec. 15, 1938, of James Wallace Esler, of Washington, D. C. Born October 27, 1894, in Tarentum, Pa., son of James M., and Katherine Esler, and educated in the public schools of Tarentum and at Washington and Jefferson College (A.B. 1916), he was graduated from the Medical School of the University of Pennsylvania in 1920. Research in physiology at the medical school, followed by two years' internship at Pennsylvania Hospital, led him in 1923 to begin the practice of medicine in his home town, and for five years he built the foundation there, and in Boston, for the special field of cardiology, which he entered in the city of Washington in the fall of 1928.

It was our privilege in Boston early in that year of 1928 to have James Esler come to us as a graduate student and research associate in the cardiac clinics and laboratory of the Massachusetts General Hospital. He revealed to us during his stay not only the ability and industry that gave promise of the career that was fulfilled in the decade to come, but also the charming personality that endeared him to all who came in contact with him.

Modest, capable, thoughtful, and patient, he established himself in Washington as a pioneer in the special field of heart disease and left a place in the medical profession there which will be difficult to fill. He was Professor of Cardiology and Associate in Medicine at Georgetown University School of Medicine, member of the staffs of the Georgetown University, Garfield Memorial, and Emergency Hospitals, past president of the Washington Heart Association, and member of the District of Columbia Medical Society, Clinico-Pathological Society, and Osler Society of Washington.

Married Aug. 12, 1929, to Miss Lillian McGlasson, of Glendale, Ky., he has handed on his name to his son, who was born in 1933.

Many of James Esler's old friends join me in this tribute to his memory.

Paul D. White

Department of Reviews and Abstracts

Selected Abstracts

Kirch, E., and Nürnbergger, W.: Development and Recession of Experimental Athlete Cardiac Hypertrophy. Arch. f. Kreislauf. 4: 1, 1939.

Studies were carried out on twenty-two rats who were subjected to swimming and running exercises. A definite hypertrophy was found which was proportional to the intensity of the exertion. With the severest exertion, the hypertrophy appeared in six days. Hypertrophy begins in the right ventricle and is most marked in this chamber. The right auricle is next involved, and usually also the left ventricle, and occasionally the left auricle. Running causes more hypertrophy of the left heart than swimming. The hypertrophy is accompanied by enlargement and elongation of the heart and involves the right heart more than the left.

In five rats, intensive exercise was carried out followed by five to six months of normal activity. In these animals, the cardiac dilatation and hypertrophy had disappeared. However, one animal showed a residual hypertrophy after 153 days of rest.

KATZ.

Rothberger, C. J., and Sachs, Arpad: Rhythmicity and Automatism in the Mammalian Left Auricle. Quart. J. Exp. Physiology 29: 69, 1939.

Mechanical records and electrograms taken from isolated strips from the left auricle of the heart of rabbits or guinea pigs show that the left auricle may beat spontaneously, although the histologic examination following the experiment fails to show specific nodal tissue in them. This examination was done by Professor Aschoff. These strips respond to stimulation by single condensor discharges or faradic current sometimes with an outlasting rhythm. Adrenaline and histamine produce sometimes, strophanthine never, and barium chloride, veratrine, and aconitine always a rhythmic activity, sometimes of long duration. In man, under pathological conditions, the left auricle may possibly initiate automatic contractions; single auricular extrasystoles or auricular tachycardias, especially those with a negative P wave in the electrocardiogram, may therefore, as Rothberger and Winterberg supposed long ago, originate in the left auricle.

AUTHORS.

Hamilton, W. F., and Dow, Philip: An Experimental Study of the Standing Waves in the Pulse Propagated Through the Aorta. Am. J. Physiol. 125: 48, 1939.

A technique is described for recording, directly and adequately, simultaneous pressure pulses from different parts of the open or occluded system comprising the aorta and the iliac and femoral arteries of intact dogs.

Series of records taken by this method present the following findings: a) The pulse pressure increases gradually from the aortic arch to the femoral, although the mean pressure remains constant.

b) The augmented systolic peak is not simply a propagated wave but is stationary. Beyond a nodal point somewhere in the thoracic aorta it occurs simultaneously at

all points in the system. The time from the start of the wave at the root of the aorta to the time of this stationary peak is a characteristic function of the length and the elastic properties of the central arteries, probably as far out as the knee.

c) Along with the formation of this stationary peak, and following it in the pulse cycle, there develop alternate falls and rises of pressure which reciprocate with simultaneous rises and falls at the root of the aorta.

d) By moving an occlusion down the aorta, the nodal point between these reciprocating divisions of the system can be shifted in the same direction.

e) The transformations in form and pressure undergone by the pulse in its travel toward the periphery are thus experimentally shown and their cause is identified. By reflection of the propagated wave, with changes in the volume-elasticity properties of the vessels through which it goes, certain components of it resonate, and the standing waves so produced are superimposed upon the fundamental pulse form.

It is shown that in the light of these experiments the application of sound physical principles permits a reconciliation of many controversial lines of emphasis in this field.

AUTHORS.

Dow, Philip, and Hamilton, W. F.: An Experimental Study of the Velocity of the Pulse Wave Propagated Through the Aorta. *Am. J. Physiol.* 125: 60, 1939.

Derived from records obtained by previously described methods, continuous curves are presented which show the changes in pulse wave velocity from aortic arch to femoral artery in seven dogs.

The wave is shown to accelerate quite evenly over this range, with considerable variation in the rate of acceleration in different dogs.

Measurements of the elasticity of rings cut from an aorta give results which are consistent with such an acceleration.

The pulse wave velocity corresponds to different functions of the diastolic pressure in the thoracic and abdominal portions of the aorta.

Stimulation of the vagus nerves, whether electrical or reflex, is accompanied by a slowing of the pulse wave in addition to that produced by the lowering of the diastolic pressure. In the records available so far, this effect is evident at low and normal pressures in the abdominal aorta and at higher pressures in the thoracic aorta.

The only hypothesis that can be put forward in explanation at present is that with vagus stimulation either nervous or hormonal influences bring about a change in the elasticity of the arterial wall by varying the tone of smooth muscle fibers.

AUTHORS.

Graybiel, Ashton, and White, Paul D.: Diseases of the Heart: A Review of Significant Contributions Made During 1938. *Arch. Int. Med.* 63: 980, 1939.

This important review summarizes briefly all the contributions made to the cardiac literature in the past year.

McCULLOCH.

Hamilton, W. F., Woodbury, R. A., and Vogt, Elkin: Differential Pressures in the Lesser Circulation of the Unanesthetized Dog. *Am. J. Physiol.* 125: 130, 1939.

A modification of the London technique for placing angiostomy cannulae upon the pulmonary vessels, an advantageous device for administering artificial respiration and the technique for making optical tracings of the pressures in the pulmonary artery and vein of unanesthetized dogs are described.

By means of differential and ordinary "hypodermic" manometers, records were made of the pressures in the pulmonary artery, and pulmonary vein, of the effective

pressures distending these vessels within the thorax and of the gradient of pressure forcing blood through the lungs.

In normal unanesthetized dogs, breathing quietly, the pulmonary arterial pressure varies between 45/12 and 28/7 mm. Hg in different dogs and averages 37/10. The mean pressure (integrated) averages about 20 mm. Hg. The pulmonary venous pressure, taken during quiet breathing, averages 3 to 12 mm. Hg.

Inspiration lowers total pressure in both the systemic and pulmonary arteries, but raises slightly the effective pressure in the pulmonary artery. The total pressure in the pulmonary vein is lowered by inspiration but the effective pressure is changed very little. The expiratory increase in systemic arterial pressure is caused partly by an increase in intrathoracic pressure and partly by an increase in cardiac output.

The gradient of pressure forcing blood through the lungs is decreased by a prolonged rise in intrathoracic pressure and increased immediately afterwards. It is also increased by air embolism. It is unaffected by this gradient. Secondary effects due to changes in blood flow are so small as to imply very definitely that the pulmonary channels are quite capacious.

The rise in pulmonary arterial pressure after large doses of epinephrine is due to back pressure from the left ventricle and is not accompanied by an increase in the gradient of pressure from artery to vein. We can supply no clear cut evidence that vasoconstriction in the pulmonary bed plays any significant role in the dynamics of the lesser circulation.

AUTHORS.

Wright, G. W., Hallaran, W. R., and Wiggers, C. J.: The Economy of Effort Index for Hearts of Normal and Hypertensive Subjects. *Am. J. Physiol.* 126: 89, 1939.

A method, based upon a principle worked out from animal experiments by Wiggers and Katz, is suggested, by which the economy of effort during ejection of the normal human left ventricle can be expressed and compared with that of the ventricle of a hypertensive subject.

Reconstruction of the ejection phase of the intraventricular pressure curve is accomplished using the subclavian pulse curve for contour and applying simultaneously obtained brachial artery pressures for the ordinate (pressure) values. The surface area of the curve above diastolic value divided by that beneath this area offers a quotient expressing the economy of ventricular effort during ejection.

Results for eighty-one normal individuals indicate a wide variation in the quotient (0.215-0.880) and it is greatest in those subjects having a comparatively large pulse pressure and a low diastolic pressure. This wide variation is explained by the normal variation in the relation of systolic discharge to peripheral resistance.

Results for fifty-four individuals with chronic hypertension show an even greater range of quotient (0.220-1.030) and the same relation to pulse pressure and diastolic pressure is observed as was found in the normal individuals. A larger number of this group had a quotient above the median (0.428) of the normal group. The conclusion is reached that the left ventricle in hypertension maintains a quotient as good as, or even better than, that of the normal left ventricle by virtue of a large pulse pressure and in spite of an elevated diastolic pressure.

Evidence is given in support of the belief that decreased distensibility of the aorta when found in conjunction with hypertension, particularly in older subjects, supplies a mechanism whereby the economy of effort during ejection remains normal or may actually become more favorable.

AUTHORS.

Leriche, René, Fontaine, René, and Friedmann, Leon: Is Stellate Infiltration in Pulmonary Embolism Justified From the Physiological, Anatomical and Pathological Points of View? What Place Should It Occupy in the Therapeutics of This Condition? *Jour. de Chirurgie* 50: 47, 1937.

The authors report treatment of three cases of pulmonary embolism by anesthetization with novocain of the stellate ganglia. Good results were noted once, failure occurred twice. They believe that vasoconstrictive reflex is set up by the embolus which in itself does not seem sufficient to cause death in many instances. They point out the differences of effect on circulation of ligation of the femoral artery and occlusion of it by an embolus, and they feel that in the latter condition there is complementary vasospasm. The authors believe that the pulmonary arteries receive their vasomotor fibers from the cardiac plexus which in turn receives many fibers from the stellate ganglia. They believe that on an average one out of each three cases of pulmonary embolism might be greatly benefited by the procedure mentioned above. They believe that all physicians should be taught to perform anesthetization of the stellate ganglia immediately in cases of pulmonary embolism.

ALLEN.

Schlomka, G., and Konigs, G.: Relative Duration of Systole. V. In Heart Muscle Disease. *Ztschr. f. Kreislaufforsch.* 30: 825, 1938.

The duration of systole is usually relatively longer when the heart muscle is damaged, especially in older people. In a few, when related to heart rate, there is an abnormal short duration of systole, and these are the ones with poorly functioning hearts.

KATZ.

Latzel, M.: Relative Duration of Systole in Hot Baths. *Ztschr. f. Kreislaufforsch.* 30: 865, 1938.

The relative duration of systole (with respect to heart rate) using the cube root formula of Fridericia, decreased in hot baths of 42° C.

KATZ.

Scherf, David, and Kisch, Franz: Ventricular Tachycardias With Variform Ventricular. *Bull. New York Medical College* 2: 73, 1939.

A series of eighteen cases of ventricular tachycardia with alternation of the form of the ventricular complexes, sometimes combined with a change or true alternation of the length of the diastoles, have been observed. They may be classified into three groups: regular alternation of two different forms of the ventricular complex and a regular rhythm; regular alternation of two forms as well as of the length of the diastoles; a complete irregularity of the form and sometimes also of the rhythm of the ventricular extrasystoles.

Comment was made upon the various explanations which have been advanced for these cases and it was shown that in every type a single center of stimulus formation may exist while the abnormal picture may be caused simply by a disturbance of intraventricular conduction. This is proven by the observation of two cases in which beats originating in the auricle were abnormally conducted to the ventricle in such a manner that all three of the types of tachycardia were imitated. The assumption that the formation of a stimulus in the ventricle itself may be followed by similar disturbances of conduction is entirely comprehensible.

Apart from very rare exceptions, myocardial changes always exists in cases of this kind. In addition the use of digitalis is found an initiating factor in a majority of the cases. Even small doses of digitalis may produce these tachycardias at times.

One case was described in which such a tachycardia was observed over a period of five years; necropsy failed to reveal any pathologic change in the heart save a marked dilatation, the consequence of the tachycardia.

AUTHORS.

Cowan, John: Some Disturbances of the Rhythm of the Heart. *Brit. Heart J.* 1: 3, 1939.

Sino-auricular block is not necessarily accompanied by cardiac symptoms. Four cases came under observation on account of symptoms other than cardiac; nine cases on account of cardiac symptoms. The heart may be apparently sound (six cases); or may show signs of organic heart disease (seven cases).

Sino-auricular block can only be recognized by polygraphic or electrocardiographic examination. It may be suspected as the cause of recurrent syncope in patients who show, between attacks, gross sinus irregularity.

The presence of sino-auricular block does not affect the cardiac prognosis or treatment in the individual case; which must be based upon the general rather than the cardiac picture.

AUTHOR.

Wood, Paul, and Selzer, A.: Chest Leads in Clinical Electrocardiography. *Brit. Heart J.* 1: 49, 1939.

The normal appearances of electrocardiograms obtained with Lead IV R have been presented.

Five other chest leads were investigated: Lead IV F; the left pectoral—right arm lead; the left pectoral—left leg lead; the right pectoral—right arm lead; and the right pectoral—left leg lead.

Limb lead and multiple chest lead electrocardiograms were obtained from 302 selected cases of heart disease, and from twelve cases of cardiac displacement due to a high diaphragm.

In addition to their value as an aid in the recognition of ischemic heart disease, chest leads have been found of service in the diagnosis of rheumatic carditis, pericarditis, left ventricular enlargement, right ventricular enlargement, acute cor pulmonale resulting from pulmonary embolism, and of doubtful or bizarre forms of bundle branch block.

The right arm was both the most informative and the most convenient site for the distal electrode; and we believe that the evidence is now sufficient to warrant its routine use in preference to the left leg. The latter was only advantageous when it was desired to distinguish left ventricular enlargement from cardiac displacement due to elevation of the diaphragm.

Multiple chest leads are of value not only because they may yield diagnostic evidence of myocardial infarction when a single chest lead is barren, but also because they are a safeguard against faulty interpretation of Lead IV, because each of the three leads (Lead IV and the two pectoral leads) used in this investigation has some special value peculiar to itself, and because a study of these three leads in relation to one another may give information which is unobtainable by a study of individual leads.

AUTHORS.

Robinson, Roger W., Contratto, A. W., and Levine, Samuel A.: *The Precordial Lead*. Arch. Int. Med. 63: 711, 1939.

A study was made to ascertain which point over the precordium could be used in taking the so-called Lead IV that would furnish the most reliable information in the diagnosis of myocardial infarction. For this purpose nine or ten tracings were taken with the electrode in various parts of the precordium in each of 352 cases. The two main criteria that were analyzed were the presence or absence of the Q wave and the direction of the T wave. In this study tracings were regarded as indicative of myocardial infarction if the Q wave was absent. They were called questionably indicative of infarction if the Q wave was less than 2 mm. deep. The term abnormal was used when a normal Q wave was present but the T wave was upright. It was found that interpretations of the electrocardiograms obtained with the electrode over the base of the heart and along the sternum were often misleading. The error decreased as the apical region was approached. It was also found that the electrocardiograms obtained with the electrode in the region of the nipple or in the midclavicular line, although generally reliable, were frequently not so when there was considerable cardiac hypertrophy. The only lead that gave a curve for which a satisfactory interpretation could be made with an extreme degree of accuracy was the one for which the electrode was placed over the apical impulse of the heart.

For seventy-five persons with normal hearts the Q wave was normally present and deepest with the apical lead. With the other positions it was often small (less than 2 mm.) and rarely absent. The T wave was frequently upright with many of the precordial positions and in four instances even with the apical lead.

Deep inspiration was found to shorten the Q wave and to change an inverted to an upright T wave in some instances. More reliable information could be obtained during normal breathing than during deep inspiration.

Although minor differences in the electrocardiograms were noted with the patient in the supine, upright, left lateral or right lateral position, these did not alter the accuracy of the interpretations with the apical lead.

It was found that when fluid was present in the left pleural cavity, an absent or small Q wave might become normal after thoracentesis.

The removal of fluid from the abdomen changed a small Q wave to a normal one.

When the heart was considerably enlarged, owing to vascular disease, hypertension or other causes, frequently there was no Q wave with any of the precordial leads except the apical. The T wave was often upright even with the apical lead.

Two patients with syphilitic narrowing of the coronary ostia without myocardial infarction showed a Q wave of only 0.5 mm. with the apical lead.

The presence of auricular fibrillation or delayed intraventricular conduction did not interfere with the correct interpretation of the fourth lead. In two of the eleven cases of left bundle branch block the method of interpretation of Lead IV used in this study was incorrect.

It can be concluded that, except in the rare instances cited, a Q wave of 2 mm. or more in the electrocardiogram with the apical position will always be found when the heart is normal or when there are various forms of heart disease unassociated with anterior myocardial infarction.

AUTHORS.

Braun-Menendez, E., and Solari, L. A.: *Ventricular Asynchronism in Bundle Branch Block*. Arch. Int. Med. 63: 830, 1939.

Bundle branch block experimentally produced in dogs is followed by marked ventricular asynchronism, and it may be assumed that the same happens in human beings with bundle branch block.

Optical recording of the apex beat, the venous pulse, the heart sounds, and the central arterial pulse simultaneously makes it possible to recognize whether or not the ventricles beat synchronously or, in the absence of synchronism, which ventricle contracts first.

Investigations carried out in this way have demonstrated that the electrocardiographic alterations which, according to the older view, were considered as characteristic of right bundle branch block are, in fact, encountered in cases of left bundle branch block.

Electrocardiograms with all the characteristics of bundle branch block may exist without there being any detectable asynchronism and hence without there being complete block.

In conclusion, it may be advanced that the electrocardiogram which shows pronounced alterations affords a good evidence of intraventricular block. However, it does not offer a reliable means for establishing a diagnosis of complete bundle branch block, or, furthermore, for the localization of the branch involved. The adequate recording of the mechanical events due to cardiac action affords the only means for determining the existence of ventricular asynchronism, thereby allowing the recognition of delayed excitation through one of the bundle branches and the localization of the functional disturbance.

AUTHORS.

Vander Veer, Joseph B., and Edwards, Joseph C.: The Significance of Small and Absent Initial Positive Deflections in the Chest Lead. *Am. J. M. Sc.* 197: 663, 1939.

The electrocardiograms and clinical histories of 102 patients with an absent initial positive deflection in the precordial lead (R wave of new and Q wave of the old technique), and forty-six patients with a small initial positive deflection (2 mm. or less) have been reviewed.

The most frequent cause of an absent initial positive deflection (67 per cent) was a previous anterior myocardial infarction. In the other patients with this abnormality, organic cardiovascular disease was present in all instances, usually arteriosclerotic or luetic heart disease, with or without hypertension. Cardiac enlargement and myocardial damage from other causes may also be factors causing disappearance of this wave.

When the initial positive deflection is absent in the precordial lead, the QRS complex rarely returns to normal. An absent initial deflection may be followed by a small initial deflection in some cases of myocardial infarction, and occasionally either of these signs may be the only residual electrocardiographic finding in this condition.

A small initial positive deflection in the precordial lead (2 mm. or less) is a less important sign than an absent one. It is occasionally seen in normal hearts but usually is of similar significance to an absent initial positive deflection.

The importance of proper application of the precordial electrode is emphasized, especially in relation to the size of the initial positive deflection of the QRS complex.

A correlation between the T-wave findings in the precordial lead and Lead I with the absent and small initial positive deflections shows a larger per cent of abnormal T waves in the absent deflection group. The presence of an abnormal T wave in one or both of these leads with a small or absent deflection in the precordial lead makes the latter sign of greater significance. In general, T-wave abnormalities are less permanent than the QRS abnormalities in the precordial lead.

AUTHORS.

Van Nieuwenhuisen, C. L. C., Hartog, H. S. Ph., and Matthijssen, E.: *New Diagnostic Features in the Four Lead Electrocardiograms of Angina Pectoris.* *Acta Scandinav. Med.* 98: 468, 1939.

This is one of a series of articles on the diagnostic points of electrocardiography. Amongst 5,500 curves, the authors selected for further study 355, presenting peculiarities which they considered suggestive of disease.

Fifty-one electrocardiograms met Pardee's criteria for deep Q_s waves. They assumed that coronary sclerosis was present in 84 per cent of these; twenty-four of them suffered from angina pectoris, twenty-four had congestive failure, eleven of them had both together.

They included W- and M-shaped complexes in Lead III, though they admitted that they were more significant in Lead II. In the presence of marked left cardiac dilatation, left axis deviation might be obscured by Pardee's Q waves or by W- or M-shaped complexes.

Sixty-three tracings showed W-shaped complexes (fifty-eight in Lead III, five in Lead II). Of these, twenty-four had hypertension, twenty-four cardiac failure, and twenty-nine angina pectoris. Seven had both angina pectoris and cardiac failure.

Ten showed M-shaped complexes (one in Lead I, three in Lead II, six in Lead III). Seven of these had some decompensation and three also angina pectoris.

More original are the observations on the "notch at the foot of the R" which the authors consider the result of a rotation of the axis of the "S," causing it to become positive. It occurred fifty-seven times, mostly in men, and above the age of 50 years. About one-half the cases had hypertension, one-third congestive failure, and one-half angina pectoris. Often there were other signs of coronary disease. It occurred most commonly in Leads I and II, rarely in III. In almost all cases presenting this change there was reason to suspect heart disease. The notch was observed to appear following coronary occlusion and, once, to precede it. Then it appeared during effort only. It was also observed following cardiac shock, just after the clonic phase.

They associated the "saddle shaped S-T segment" with myocardial changes, but they failed to define it accurately. In some cases they considered it a less developed form of the preceding change, and they surmised that the two irregularities had a common cause. The saddle shaped S-T segment occurred in 102 cases, in sixty-six of these they thought other clinical data justified a diagnosis of coronary sclerosis, and in ten others there was evidence of other heart disease. In many cases the patients had what appeared to be functional complaints. The authors seemed less certain of the significance of this finding; certainly in the absence of control material or autopsy findings, this point requires further study.

T waves exceeding in height one-half of the R waves in the same standard had occurred in twenty-seven tracings. Eight complained of angina pectoris, five of congestive failure. Coronary sclerosis was thought to be present in fourteen. In the absence of thyrotoxicosis and mitral stenosis, the authors considered "tall T waves" an important sign.

Chest leads were taken with the right arm electrode in fourth left intercostal space and with left leg electrode. The changes seen in coronary thrombosis may also be seen in coronary sclerosis, possibly indicating a similar but slower process. Dilatation of the left ventricle may cause a shallow Q wave, unless the electrical axis takes a longitudinal position (youth, mitral stenosis). Shallow Q waves may also result from coronary sclerosis. Deep Q waves in the chest lead, in the absence of a longitudinal axis in the standard leads, indicate coronary sclerosis. Deep Q waves in the chest leads occurred in forty-five patients. Twenty patients had

congestive failure, eighteen angina pectoris. In thirty-one, coronary sclerosis was obvious, so the authors considered this sign important.

Appended is a large collection of electrocardiograms. The suggestions contained in this paper are stimulative, but require definitely further checks and controls before they can be accepted.

JENSEN.

Allen, Arthur C.: Mechanism of Localization of Vegetations of Bacterial Endocarditis. Arch. Path. 27: 399, 1939.

In from 50 to 75 per cent of cases bacterial endocarditis is superimposed on rheumatic endocarditis. Rheumatic endocarditis commonly produces a valvular fibroplastic deformity with stenosis. This lesion takes the form of a projecting shelf or barrier, usually at the line of closure, against which the blood stream strikes. By virtue of this obstruction to the systolic discharge (manifested by myocardial hypertrophy) the site of the deformity suffers a distinctly greater impact and contact than the normal valve leaflet, which "gives" or yields with the stream. This contact with the blood (and organisms in a bacteremia) is further enhanced by the diastolic backflow due to insufficiency, the usual concomitant of stenosis. The role of these dynamics in the localization of vegetations is suggested.

This same mechanism applies to congenital lesions including the "so-called congenitally bicuspid aortic valve."

Attention is called to the fact that the outflow surface of all valves, normal or deformed, comes in contact with a much greater area of blood (and toxic agents) than the opposite surface. The significance of this in the localization of vegetations is stressed.

An explanation based on the same principles is offered for the rarity with which auricular fibrillation is complicated by bacterial endocarditis. The possibility of the influence of other auxiliary factors is not precluded.

It is pointed out that there is an increased tendency for acute rather than subacute endocarditis to occur on (a) valves not previously deformed and (b) valves of the right side of the heart. This fact is correlated with the principles of impact and contact.

AUTHOR.

Stewart, Harold J., and Heuer, George J.: Chronic Constrictive Pericarditis. Arch. Int. Med. 63: 504, 1939.

An analysis of the clinical manifestations in nine cases of chronic constrictive pericarditis has been given. In seven of these cases partial pericardiectomy was performed. The presence of this syndrome should be considered when there are signs of congestive heart failure in the absence of the usual causes of failure. Three of the patients appear to be "cured"; three others are greatly improved, and the seventh is now convalescing from the operation. Studies of the circulation have shown that this syndrome is associated with a decrease in the cardiac output per minute and per beat, a rise in the venous pressure and a slowing of the velocity of the blood flow. These alterations are related to the obstruction to the flow of blood into the heart, i.e., to interference with diastolic filling, and to interference with contraction, by the thickened, adherent pericardium. With the institution of pericardial resection and the subsequent clinical improvement, the measurements of the circulation undergo parallel changes toward or to normal. There is parallelism in these cases between the clinical manifestations and the objective measurements of the circulation. Experience in these cases leads the authors to recommend surgical treatment.

AUTHORS.

Woodbury, R. A., Robinow, M., and Hamilton, W. F.: Blood Pressure Studies on Infants. *Am. J. Physiol.* 122: 472, 1938.

Optical registrations of arterial pressure pulses were obtained by the "hypodermic manometer" from thirty-seven newborn babies. The same systolic values could be obtained by cuff and palpation if the arm band was 2.5 cm. wide. The conventional cuff of pediatricians gave systolic readings 20 to 25 mm. Hg too low.

The blood pressures of twenty-four full term newborn infants averaged 80/46 mm. Hg. The standard deviation of a single observation was 8.1 mm. Hg (systolic) and 8.2 mm. Hg (diastolic).

The infant's blood pressure was found to be not significantly affected by the following: 1, obstetrical anesthesia; 2, the onset of respiration; 3, clamping the cord after birth, and 4, administration of $\text{CO}_2\text{-O}_2$ to the baby.

The infant's blood pressure was affected slightly but significantly by the following: 1, blood pressure level of the (normal) mother $r = 0.303 \pm 0.063$ (diastolic); 2, toxemia of pregnancy (+10 mm. Hg systolic, +3 mm. Hg diastolic); 3, amyl nitrite administered to baby (-8 mm. Hg systolic, -7 mm. Hg diastolic), and 4, epinephrine, intravenously, 0.2 mg. (+10 mm. Hg systolic, +7 mm. Hg diastolic).

The infant's blood pressure was markedly affected by the following: 1, crying (+10 to 45 mm. Hg systolic and diastolic); 2, dehydration without collapse (+30 mm. Hg systolic); 3, administration of fluid to dehydrated babies (-30 mm. Hg systolic); 4, age of infant, and 5, degree of prematurity.

AUTHORS.

Gavey, C. J., and Parkinson, John: Digitalis in Heart Failure With Normal Rhythm. *Brit. Heart J.* 1: 27, 1939.

This investigation was undertaken primarily to decide the clinical value of digitalis in heart failure with normal (sinus) rhythm. The secondary purpose was to compare its value in such failure with that in auricular fibrillation, which is better known.

Sixty-five patients with heart failure and normal rhythm were observed. After one week or more at rest in bed, digitalis leaf was given in a dose of 2 grains three times a day, i.e., 6 grains (0.4 gm.) daily, for one to two weeks. The condition at the beginning of digitalis treatment was compared with that at the end. The criteria of failure were dyspnea, liver enlargement, and edema with or without hydrothorax; and judgment as to improvement was made on these criteria together with diuresis. Reduced heart rate was not reckoned as a criterion, and it is separately considered. Twenty-five patients had hypertensive heart disease, 12 with and 13 without past coronary thrombosis; 11 had chronic rheumatic valvular disease; 9 had syphilitic heart disease; and 2 were unclassified. In these, the main groups, the majority, 72 per cent, had edema at the end of the week's rest in bed and a quarter of these had hydrothorax, confirmed by x-ray examination.

The control lay in the preliminary rest in bed without digitalis; but for comparison another series of 30 patients with failure and auricular fibrillation was observed in the same way.

Under rest in bed only, in normal rhythm, 17 of 47 (36 per cent) improved; in auricular fibrillation, 11 of 28 (39 per cent) improved.

The main digitalis results are shown by a table, and there are illustrative charts of effect and of failure of effect. In normal rhythm some clinical improvement was demonstrated in 35 out of 58 tests (60 per cent); and 23 of 58 showed none. Admittedly 17 received only slight benefit, so that moderate or great benefit resulted in 18 only, i.e., 31 per cent of the whole. There was little difference in response among the separate etiological groups, though the rheumatic group responded best.

The heart rate in failure with normal rhythm is moderate, the average in our series before digitalis being 85. It was reduced by digitalis in 27 out of the 58 tests (47 patients), i.e., in almost half (46.5 per cent). The average fall in rate among those in whom it occurred was from 85 to 67, i.e., 18. This was usually secured without toxic symptoms, and when these appeared (20 per cent) they were slight (nausea and rarely vomiting). Whatever the initial rate, digitalis often reduced it. Reduction in rate was not always accompanied by clinical improvement, though improvement was rather more common in the patient who showed it. Some good clinical results were seen without any reduction in rate.

Diuresis was induced by digitalis in 27 of 58 tests (47 patients) in normal rhythm. It was freer in patients with gross edema than in those with little or none; but some diuresis was obtained almost as frequently in those without as in those with edema.

The course of the disease after the onset of failure in normal rhythm is short—18 of 29 patients died within a year—and this in general must lessen the likelihood of improvement from digitalis. Yet in a particular patient the response to digitalis is no guide to the expectation of life; and if digitalis fails at a first trial, it may occasionally succeed at a later trial.

Of the patients with auricular fibrillation, 12 had hypertensive heart disease, 14 had chronic rheumatic valvular disease, and 4 were unclassified. Clinical improvement was demonstrated in 23 of 32 tests (30 patients), i.e., in 72 per cent; and 9 showed none. It was slight in nine, and moderate or great in fourteen, i.e., 44 per cent of the whole.

The heart rate was higher than in the normal rhythm series, an average of 98 against 85, a difference of 13. The rate was reduced by digitalis in the great majority, in 28 of 32 tests (87 per cent). The average fall in rate where a fall resulted was from 100 to 70, an average fall of 30. Most of those with slowing also showed benefit, but in the absence of slowing there was none.

The rheumatic group was distinguished by a higher average rate before treatment, by reduction of the rate in all fourteen cases, and by clinical improvement in all but two. Even with a moderate initial rate (below 100), results were better in rheumatic than in nonrheumatic fibrillation, though no better than in rheumatic cases with normal rhythm.

Without the rheumatic group, the fibrillation series responded to digitalis no better than the normal rhythm series. In hypertension, for instance, the results were similar.

A mercurial diuretic sometimes administered after a digitalis test nearly always produced a free diuresis even where digitalis had failed. In edematous patients other than those with rheumatic auricular fibrillation and a high ventricular rate, a mercurial diuretic usually has more value than digitalis. Yet a trial of digitalis cannot be omitted, for it alone acts directly on the heart. The partnership of a mercurial diuretic with digitalis should govern the treatment of heart failure.

Digitalis is always indicated in congestive heart failure irrespective of rhythm, but it is often inefficient, as it fails completely in about a third of all cases.

In heart failure with normal rhythm digitalis is helpful in rather more than half the cases.

In heart failure with auricular fibrillation, digitalis is more often helpful than it is in normal rhythm, for it benefits more than two-thirds. This superiority rests on its particular value in rheumatic heart failure with fibrillation, largely but not entirely due to the high ventricular rate. Incidentally, it is in this group that rate control by continued digitalis best prevents recurrence of the failure.

The real difference in the response of heart failure to digitalis lies not between auricular fibrillation normal rhythm, but rather between rheumatic auricular fibrillation and all other kinds of heart failure irrespective of rhythm.

AUTHORS.

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**Executive Committee.*

The American Heart Journal

VOL. 18

AUGUST, 1939

No. 2

Original Communications

THE ELECTROCARDIOGRAPHIC PICTURE OF EXPERIMENTAL LOCALIZED PERICARDITIS

HOWARD B. BURCHELL, M.D.,* ARLIE R. BARNES, M.D.,† AND
FRANK C. MANN, M.D.‡
ROCHESTER, MINN.

IN ELECTROCARDIOGRAPHIC studies on dogs, in which the pericardium had been opened for various reasons, certain postoperative changes occurred almost routinely and in a stereotyped manner. The chief effect has previously been noted by two of us (Barnes and Mann¹) and, in brief, consists in high, upright, peaked T waves, attaining their maximum in the period from the fifth to the tenth day after operation. It was early noted that if the pericardiotomy had been done on the left side the effect was mainly in Lead I, and if on the right side, mainly or wholly in Leads II and III. Procedures on the left side did not produce much change in Lead IV (Wolferth), but if done on the right, very deep, accentuated T waves were frequently seen. From the similarity of these waves to the electrocardiographic picture in acute pericarditis in man, it was easy to suppose that they were of similar origin.

The normal electrocardiogram of the dog varies greatly in respect to the T pattern; in general, the most stable electrocardiogram is one with T negativity in all leads. The changes in the electrocardiograms to be described are not in all cases as important with respect to their form, as with respect to the fact that they are predictable and constant over the period of their presence.

Three causes have been suggested for the electrocardiographic changes in acute pericarditis: mechanical compression of the heart by fluid, an inflammatory process involving the myocardium, and a change in the neuromyocardial balance. Scott, Feil, and Katz,² after observing R-T elevation in a case of pericarditis and in another of hematopericardium, suggested that the etiologic factor concerned is one of coronary insufficiency produced by the pressure of the pericardial fluid on the coronary

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Received for publication Dec. 29, 1938.

arteries and coronary sinus. Their hypothesis was substantiated by obtaining somewhat similar tracings experimentally in dogs by forcing fluid into the pericardial sac.² This work has been confirmed by the observation of Herrmann and Schwab,³ in experiments on goats, that increasing the pressure in the pericardial sac causes elevation of the S-T segment. In patients not suffering from an evident acute compression of the heart, it is difficult to see the counterpart of these experiments. Vander Veer and Norris⁴ found no relation between the amount of fluid and the electrocardiographic changes in man, and microscopic study of the hearts in all cases in which there was a "positive" electrocardiogram showed definite subepicardial myocarditis.

Fowler, Rathe, and Smith,⁵ studying the effect upon the electrocardiogram of occlusion of small arterial branches in the dog's heart, observed quite constant changes. In control experiments in which the pericardium had been opened, without coronary artery ligation, similar electrocardiographic changes frequently occurred. This was shown on histologic study to have been accompanied invariably by an inflammatory process involving the superficial myocardium. They advanced the conception that in both instances the electrocardiographic changes were due to the same process, namely, a superficial myocardial injury. Many of their tracings published at that time are very similar to those obtained by Barnes and Mann,¹ and to those presented in this paper.

The role played by cardiac nerves is obscure; the evidence that they might play any part lies in the following facts. Otto⁶ found that if the coronary artery supplying the wall of the right ventricle is ligated, stimulation of the right accelerator nerves accentuates the electrocardiographic picture, but stimulation of the left accelerator nerves causes the electrocardiogram to return toward normal. Similarly, with ligation of the coronary artery supplying the wall of the left ventricle, the electrocardiographic picture is accentuated by stimulation of the left accelerator nerves, and modified toward normal by stimulation of the opposite accelerator nerves. Pezzi, Defrise, and Agostoni⁷ discovered that Smith-Pardee waves in dogs disappear after arteriectomy of the ligated vessel. Leriche and his co-workers⁸ reported high, upright T waves, particularly in Leads II and III, and increase in sinus arrhythmia, after stellate ganglionectomy in dogs. We have observed similar, high, peaked T waves in the standard leads after stellate ganglionectomy in dogs, and have reproduced the same changes by injection of alcohol into the stellate ganglia without opening the chest. Somewhat similar high T waves in Leads II and III have been seen frequently by us in dogs under ether anesthesia. These changes have not been present in man following bilateral stellate ganglionectomy for Raynaud's disease in the one case observed by us.

If it were true that the electrocardiographic picture of acute pericarditis were due to a superficial myocardial inflammation, a region of

inflammation restricted to one portion of the pericardium might be localized by the electrocardiogram in the same manner as myocardial infarction may be localized. It was found that if the unopened pericardium was oversewn loosely with chromic catgut, there developed a region of pericarditis which remained localized. At the operation, a matting of catgut overlying a normal epicardium was produced, which caused inflammation of the pericardium and epicardium, with foreign body reaction and adhesions of varying degrees of permanence.

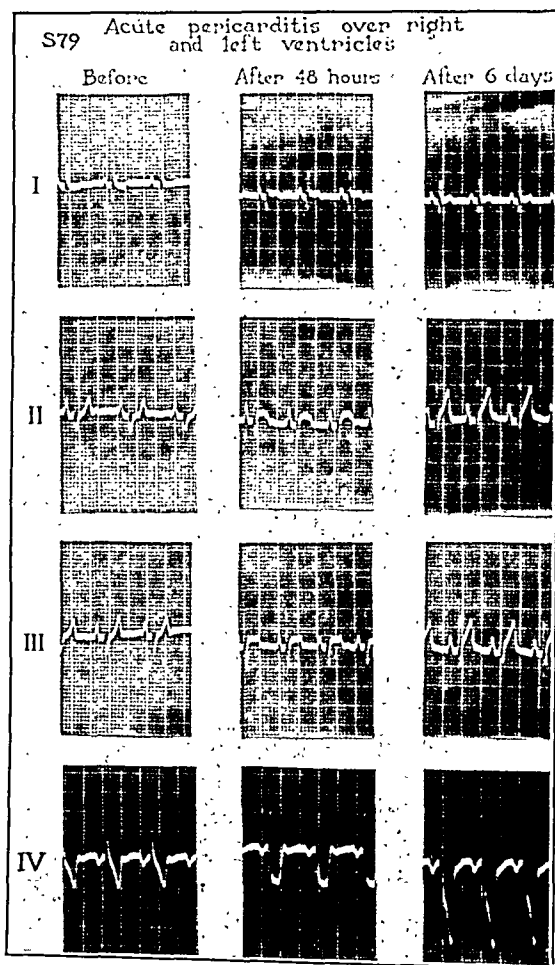


Fig. 1.—Electrocardiograms before and after experimental production of bilateral pericarditis.

The experiments were arranged as follows:

1. In two dogs the parietal pericardium was operated on bilaterally. The chest was opened through an intercostal incision on one side, the pericardium on that side oversewn with catgut, the chest closed, and the dog turned over and the procedure repeated on the opposite side.
2. In three dogs the operation was performed on the right side only.
3. In three dogs the operation was performed on the left side only.
4. In one dog, the parietal pericardium was operated on unilaterally; the evolution in the electrocardiographic pattern was observed and, when it had returned to normal, operation was performed on the other side.

5. The electrocardiographic appearance following coronary ligation, as modified by the appearance of pericarditis, was studied in many instances, and two examples were chosen for presentation.

All the operative procedures were carried out under ether or intravenous anesthesia with positive pressure insufflation of the lungs. Surgical technique was used throughout in all the operations. All the animals remained well and physically active, had no roentgenographic evidence of cardiac enlargement, and maintained normal venous pressures, measured directly by a manometer. The general well-being of the animals, absence of enlargement of the pericardial shadow, and undisturbed venous pressures are taken as evidence that pericardial fluid, as cardiac tamponade, was playing no part in the electrocardiographic picture obtained.



Fig. 2.—Superficial interstitial myocarditis as a result of experimentally produced pericarditis.

In the first group of dogs, those with bilateral pericarditis (Fig. 1), there was an early, flat or dome-shaped elevation of the S-T segment in all the standard leads, with depression of the segment in the chest lead (Wolferth). In the one dog this was more striking than in the other. This elevation gradually disappeared on the third day, being replaced by positivity of the T waves in the standard leads and deepening of the T wave in the chest lead. The T waves in the second and third leads increased in amplitude until the seventh day, and were associated with a high take-off of the S-T segments in those leads. Thus the picture of pericarditis in the human electrocardiogram was quite well reproduced, although the elevation of the S-T segment never reached the same

magnitude as that seen in the human cases. One dog was killed on the seventh day for study of the myocardium and pericardium. Extensive, but localized, regions of a granulomatous inflammation were present between the pericardial surfaces, which, however, could be quite readily separated. The inflammatory exudate extended into the superficial muscle bundles, so that there was no doubt that a superficial interstitial myocarditis was present (Fig. 2). The electrocardiogram of the other dog returned to normal on the fourteenth day. The animal was killed three weeks after the operation, and the only remaining findings were firm, fibrous adhesions, with slight epicardial thickening, in two localized regions over each ventricle.

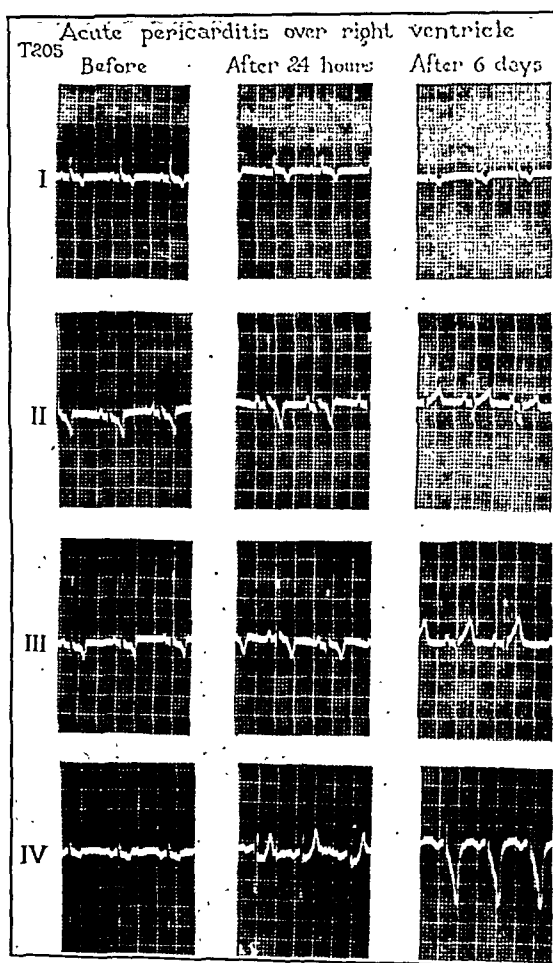


Fig. 3.—Electrocardiograms before and after experimental production of pericarditis over right ventricle.

In the second group of dogs, those with pericarditis on the right side (Fig. 3), there was an early, slight, horizontal elevation of the S-T segment which was limited to Leads II and III. By the fourth day there was a gradual change of the T waves in these leads to the upright type, with a deepening of the T wave in the fourth lead (Wolferth). The T waves

increased in size, usually had a peaked appearance, and were associated with a high take-off of the S-T segment. The greatest magnitude of the changes was generally reached on the seventh day. The T wave in Lead I remained unaffected. One of the dogs was killed on the seventh day for study of the inflammatory process. The pathologic processes in the other dogs were studied after their electrocardiograms had returned to normal.

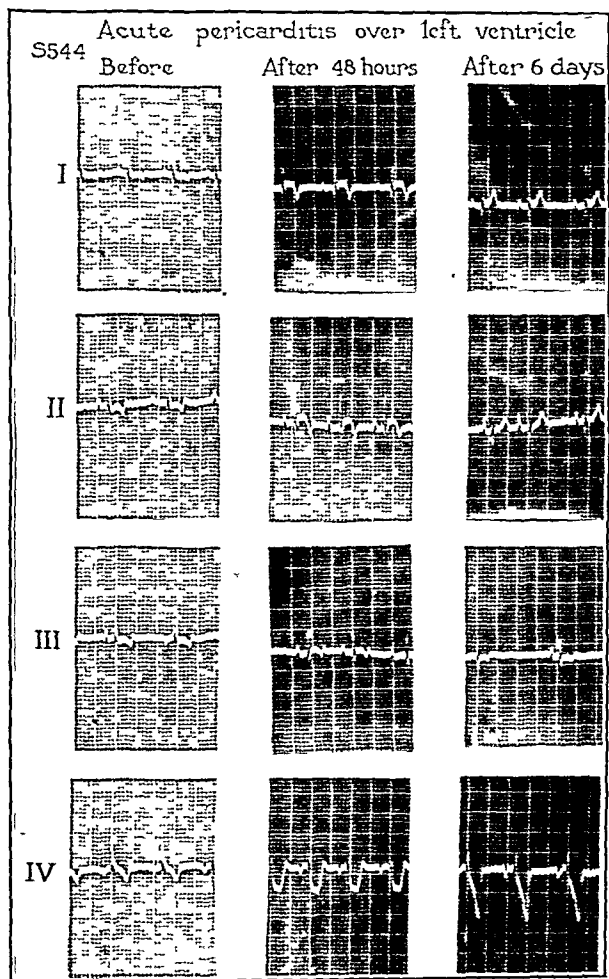


Fig. 4.—Electrocardiograms before and after experimental production of pericarditis over left ventricle.

In the third group, those with “left-sided pericarditis” (Fig. 4), there was generally an analogous slight tendency for early elevation of the S-T segment, which was limited to, or predominant in, Leads I and II. At the twenty-four-hour period there was a low S-T interval with a positive T wave in the fourth lead. This type of tracing in the Wolferth lead not uncommonly occurs at this early period in many operations on the heart, and it is deemed of significance only when considered in relation to the standard leads. In the animals of this third group the T waves in Lead I later became upright, with an associated high S-T take-off, but the change was never as striking as in Lead III with the lesion

on the right side. The electrocardiographic changes increased gradually and attained their maximum on about the seventh day, with return to normal by about the fourteenth day. In this group also, one dog was killed when the changes were thought to be greatest, and the others allowed to live until after the electrocardiograms had returned to normal. The pathologic findings in the dogs of the second and third groups were in all respects similar to those described for the first group, except that the inflammatory process was localized to the wall of one or the other ventricle. The superficial myocarditis was evident in all the dogs examined when the electrocardiographic changes were present.

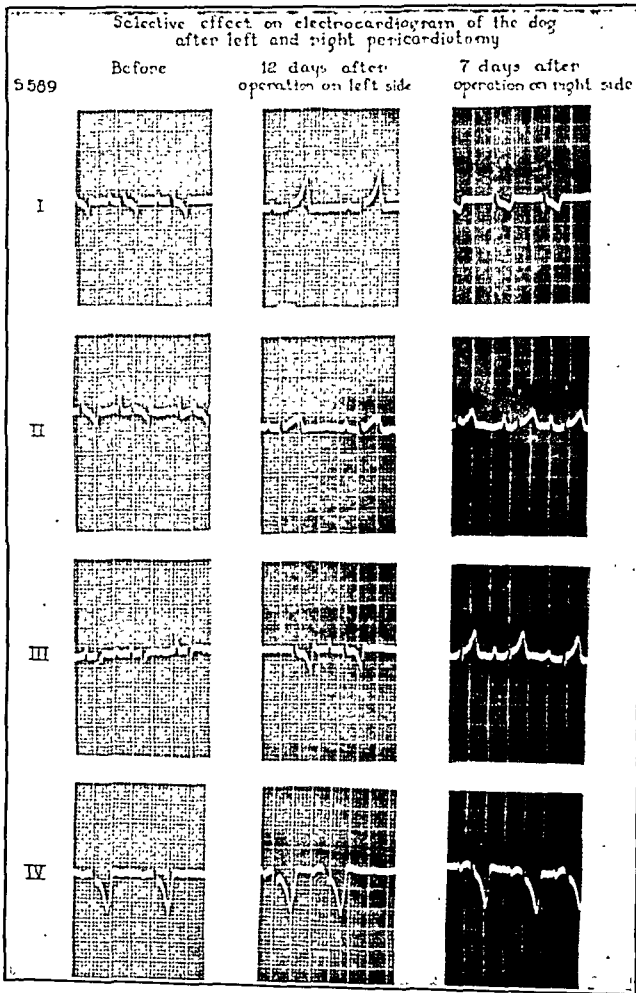


Fig. 5.—Electrocardiograms before experimental production of pericarditis, after production on left side, and after production on right side.

In the dog on which operation was performed on each side, with an intervening time period during which the electrocardiogram returned to normal, the electrocardiographic change was particularly striking (Fig. 5). After the first operation the high, peaked T waves, with elevation of the segment, were present predominantly in Lead I, while after

the second operation, on the other (right) side, the characteristic changes occurred in Lead III. Lead II was affected to a lesser extent, but in a similar way, in both instances. The electrocardiographic changes in this dog are representative of those in many dogs whose pericardiums had been opened on each side on successive occasions.

When coronary occlusion has been produced, the electrocardiographic pattern shows, after the fourth day, superimposed features which we believe are characteristic of acute pericarditis (Figs. 6 and 7). In the

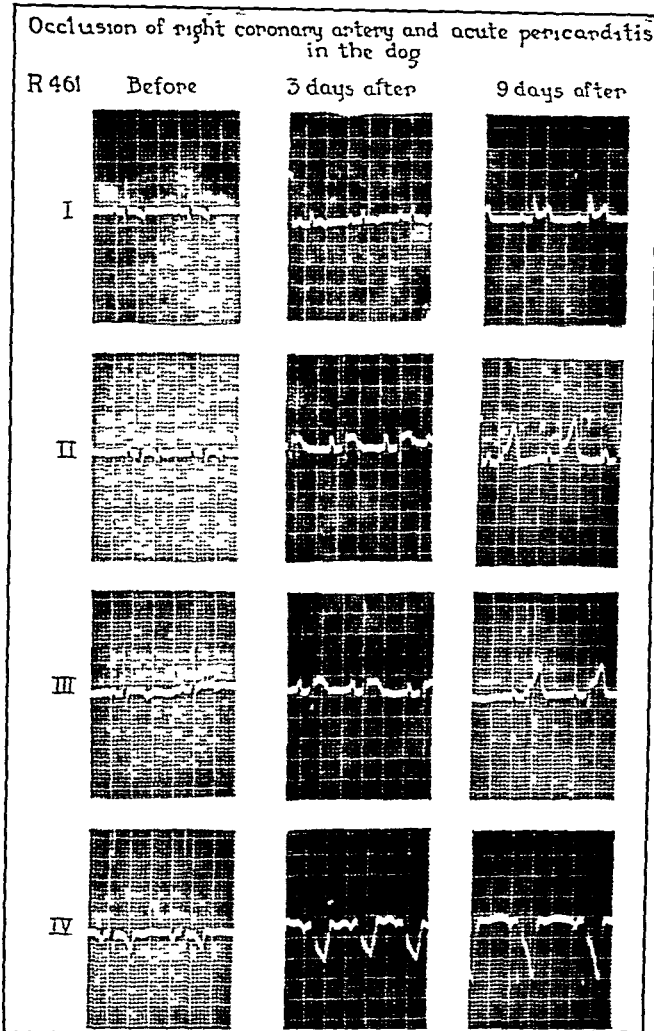


Fig. 6.—Electrocardiograms before and after occlusion of right coronary artery and acute pericarditis.

middle tracing of Fig. 6, the characteristic electrocardiogram of occlusion of the right coronary artery is present, except for depression of the RS-T interval in Lead I. It is possible that at this time the effect of the early pericarditis had already projected itself into the electrocardiogram by raising the RS-T interval to normal in this lead. On the ninth day, peaked T waves with a high RST interval were present in all the standard leads. The dog, when examined on the post-mortem table the follow-

ing day, showed a generalized fibrinous pericarditis and occlusion of the right coronary artery, but no gross infarction of the wall of the right ventricle.

Electrocardiographic tracings taken after occlusion of the anterior descending branch of the left coronary artery are to be seen in Fig. 7. The early picture is to be compared with that in Fig. 4, which illustrates the effect of pericarditis over the left ventricle only. The upright, peaked T wave in Lead I in the last tracing from this dog is unassociated

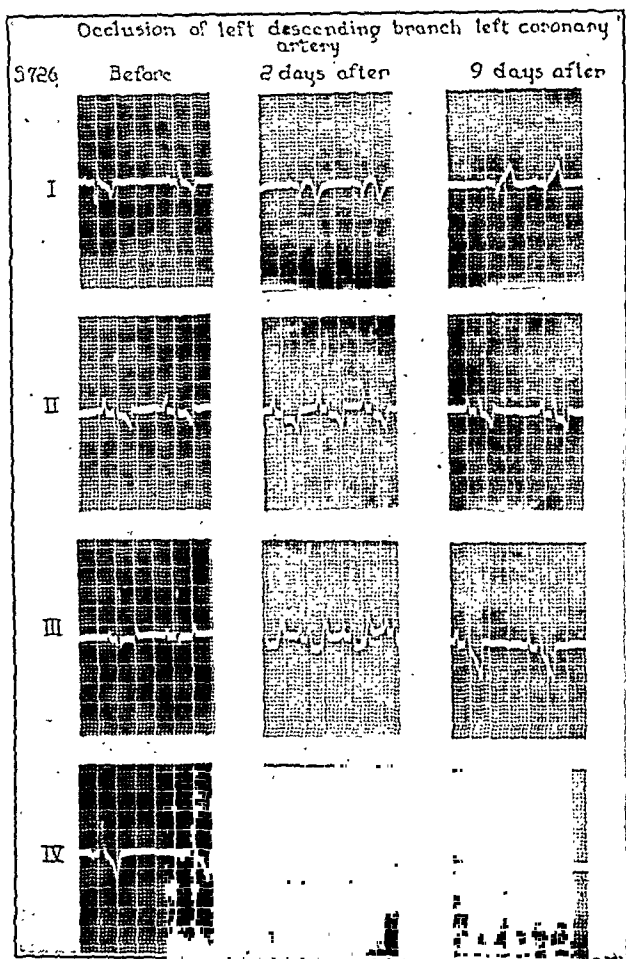


Fig. 7.—Electrocardiograms before and after occlusion of anterior descending branch.

with a similar change in Lead II. This behavior of T may be due to pericarditis, or it may be an expression of healing of the infarct, independent of pericarditis.

There were available for these studies two pairs of litter mates, each pair having similar and remarkably constant control electrocardiographic tracings. In one of each pair the pericarditic lesion was produced on the right side, while in its mate the left side was operated on. The contrasting changes in the electrocardiogram of the right-sided and left-sided

pericarditic picture were more evident in these than in other pairs of dogs not of the same litter.

That the electrocardiographic tracing of localized pericarditis was stable at given stages was evidenced, in part, by the fact that its form was not changed by the intravenous administration of adrenalin or acetylcholine. Both of these drugs frequently cause high T waves in Leads II and III in the normal dog. Digitalis (8 cat units in forty-eight hours) was given to three of the dogs, which weighed between 8 and 10 kg. There was no obvious effect in one dog, but in the other two the

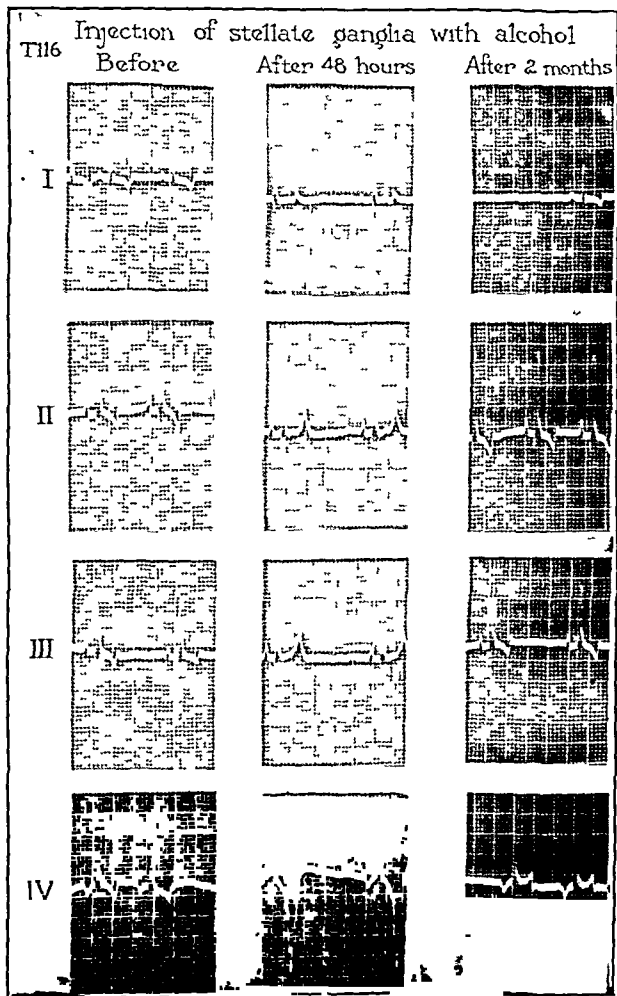


Fig. 8.—Electrocardiograms before and after injection of alcohol into stellate ganglia.

accentuated, upright T in Lead I, due to pericarditis, became negative after the full dose. There was a definite but less marked effect in Leads II and III.

COMMENT

In these experiments we have introduced further evidence that the electrocardiographic picture of pericarditis is due to a subepicardial myocarditis. It is believed that, in the experiments presented, cardiac

compression played no part. It is with some hesitation that a comparison is drawn between the electrocardiographic picture following injection of alcohol into the stellate ganglia in the dog and that of acute pericarditis. However, the close similarity of the tall, peaked T waves seen in the two conditions (compare Fig. 4, third tracing, with Fig. 8, second tracing) and certain similarities observed in the T wave in the precordial lead attract attention. The possibility that a neurogenic mechanism might play some role in the electrocardiographic changes observed following pericardial injury has to be kept in mind. It is of note that both the dogs with pericarditis and the dogs whose stellate ganglia had been injected or removed showed an increase in sinus arrhythmia. In this paper the cause of the electrocardiographic picture of chronic pericarditis in man is not discussed, although certain of the etiologic factors which are considered might be pertinent to its development.

If pericarditis produces varying electrocardiographic effects dependent on the region of its greatest localization, we have perceived the possibility of certain clinical applications. Among other things, it suggests that the picture of coronary thrombosis in man, complicated by pericarditis, as described by one of us (Barnes⁹) (elevated RS-T segments in all the standard leads), is due to a pericarditis that is not localized. Acute pericarditis complicating infarction of the posterior wall of the left ventricle in man may spread to involve the adjacent portion of the wall of the right ventricle or to the anterior wall of the left ventricle. Similarly, pericarditis associated with infarction of the anterior wall of the left ventricle may extend over the adjacent part of the wall of the right ventricle or to the posterior wall of the left ventricle. Since pericarditis localized to the region of the left ventricle in dogs has been shown to produce an elevation of the RS-T segments solely, or predominantly, in Leads I and II, and since acute infarction of the anterior wall of the human left ventricle tends to produce a similar displacement of the RS-T segment of Lead I, or of Leads I and II, it is possible that pericarditis localized in the region anterior to the left ventricle and complicating acute infarction of the wall of the left ventricle in man might not be indicated by electrocardiographic changes. For a like reason, it is possible that pericarditis confined to the region of the left ventricle and complicating acute infarction of the posterior wall of the left ventricle in man might not be reflected in the electrocardiographic pattern. The question arises whether tall, peaked T waves appearing in the evolution of the electrocardiographic pattern of acute myocardial infarction signify involvement of the myocardial layer contiguous to the epicardium, either because the infarct extends to involve the full thickness of the ventricular wall or because it is confined to the outer portion of the ventricular muscle.

It is to be noted that, in these experiments on localized acute pericarditis, the walls of the right and left ventricles of the dog have

generally acted as units, and by analogy from experiments on coronary ligation, would be expected to correspond to the anterior and posterior walls of the left ventricle in the human.

Another application of the electrocardiographic localization of superficial myocarditis may be considered. It is known that the electrocardiographic pattern of acute pericarditis may be associated with invasion of the pericardium by a malignant lesion. It would be expected that occasionally the site of this invasion, if localized, might be reflected by the electrocardiographic changes produced.

CONCLUSIONS

Evidence has been presented that the electrocardiographic picture of acute pericarditis is attributable to subepicardial myocarditis.

Localized pericarditis has been produced in dogs and characteristic electrocardiographic patterns obtained.

REFERENCES

1. Barnes, A. R., and Mann, F. C.: Electrocardiographic Changes Following Ligation of the Coronary Arteries of the Dog, *AM. HEART J.* 7: 477, 1932.
2. Scott, R. W., Feil, H. S., and Katz, L. N.: The Electrocardiogram in Pericardial Effusion. I. Clinical, *AM. HEART J.* 5: 68, 1929.
Katz, L. N., Feil, H. S., and Scott, R. W.: The Electrocardium in Pericardial Effusion. II. Experimental, *AM. HEART J.* 5: 77, 1929.
3. Herrmann, George, and Schwab, E. H.: Some Experimental and Clinical Electrocardiographic Observations on R-S-T and T Changes in Pericarditis, *Tr. A. Am. Physicians* 49: 229, 1934.
4. Vander Veer, J. B., and Norris, R. F.: The Electrocardiographic Changes in Acute Pericarditis: a Clinical and Pathological Study, *AM. HEART J.* 14: 31, 1937.
5. Fowler, W. M., Rathe, H. W., and Smith, F. M.: The Electrocardiographic Changes Following the Ligation of the Small Branches of the Coronary Arteries, *AM. HEART J.* 8: 370, 1933.
6. Otto, H. L.: The Extracardial Nerves. IV. An Experimental Study, *AM. HEART J.* 4: 64, 1928.
7. Pezzi, C., Defrise, A., and Agostoni, G.: L'onde en dome, coronarienne de Smith et Pardee chez le chien recherches expérimentales, *Arch. d. mal. du coeur* 30: 929, 1937.
8. Leriche, R., Fontaine, R., and Kunlin, J.: L'influence de la stellectomie, spécialement de la stellectomie droite, sur l'électrocardiogramme du chien, *Compt. rend. Soc. de biol.* 110: 723, 1932.
9. Barnes, A. R.: Electrocardiographic Pattern Observed Following Acute Coronary Occlusion Complicated by Pericarditis: Report of Cases, *AM. HEART J.* 9: 734, 1934.

THE PROGNOSIS OF INTRAVENTRICULAR BLOCK^o

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IN THE past few years the prognosis of intraventricular conduction defects has received considerable attention. It was the prevailing belief until recently that the presence of intraventricular block was a very serious omen. Now it is becoming recognized, as a result of the increasing use of electrocardiography as a clinical aid, that the lesion itself is not necessarily of grave importance.

The pathogenesis of intraventricular block has recently been summarized admirably by Yater.¹ Graybiel and Sprague² and King,³ among others, state that most of their patients died within fourteen months after the cardiac lesion was first recognized. However, Wood et al.,⁴ concluded that, in the absence of other signs of heart disease, bundle branch block is not necessarily an ominous sign. Sampson and Nagle⁵ then pointed out in their follow-up series that although there is a high mortality rate in the first year after discovery of the lesion, a remarkable diminution in the mortality rate occurs in those patients who survive this period. Bishop,⁶ in the most recent survey, is in accord with this conclusion.

We have recently conducted a follow-up study of private and service patients with intraventricular block whose records were made at the Michael Reese Heart Station during the past eight years. We present our results to extend and assist clarification of the prognostic survey.[†]

In our series we were able to obtain complete data on 126 patients whose electrocardiographic tracings were interpreted as showing intraventricular block. Our criterion of intraventricular block is a QRS interval of longer than 0.11 second's duration. We have been using the following classification for the past several years in order to avoid the polemic as to location of the conduction defect:

1. In intraventricular block of the common bundle branch type the QRS is upright in Lead I and inverted in Lead III, the amplitude of its major phase is more than 5 millivolts, and the T wave (with or without the S-T segment) is deviated in a direction opposite to the major phase of the QRS deflection in these leads.

2. In intraventricular block of the uncommon bundle branch type the QRS is inverted in Lead I and upright in Lead III, the amplitude of its major phase is more than 5 millivolts, and the T wave (with or without

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*Aided by the A. D. Nast Fund for Cardiac Research.

Received for publication Dec. 22, 1938.

†Not included in this series are patients with short P-R intervals or transitory intraventricular block.

the S-T segment) is deviated in a direction opposite to the major, or final, phase of the QRS deflection in these leads.

3. In intraventricular block of indeterminate (a) concordant type, the QRS deflections are all in the same direction in the three limb leads, usually upright, and the amplitude of the major phase is more than 5 millivolts, (b) S type, the QRS is diphasic and the prolongation is confined chiefly to the second phase (and the amplitude of its major deflection is more than 5 millivolts), and (c) arborization type, the major deflection in each of the limb leads is less than 5 millivolts in height.

We have used the above classification because investigations have shown that the direction of the QRS complex is determined by other factors than the block and, therefore, cannot be readily employed by itself in determining which bundle branch is involved.⁸

The data on these patients were obtained from the information on file in the Heart Station, from the patients' hospital or clinic records, and from information supplied by their private physicians and by a follow-up investigation carried out on service patients by the Social Service Department. The data of our analyses are summarized in Tables I to IV.

TABLE I
AGE DISTRIBUTION OF PATIENTS WITH INTRAVENTRICULAR BLOCK

AGE GROUP	NUMBER LIVING AT TIME OF SURVEY	NUMBER DEAD AT TIME OF SURVEY	TOTAL NUMBER	PER CENT DISTRIBUTION OF ALL CASES
20-30 yr.	2	2	4	3
30-40 yr.	2	1	3	2
40-50 yr.	7	12	19	15
50-60 yr.	14	16	30	24
60-70 yr.	20	32	52	42
70-80 yr.	6	11	17	13
> 80 yr.	0	1	1	1
Total	51	75	126	

TABLE II

PATIENTS WITH INTRAVENTRICULAR BLOCK DISTRIBUTED WITH REGARD TO DURATION OF LIFE AFTER LESION WAS FIRST RECOGNIZED IN THE ELECTROCARDIOGRAM

LIVING UP TO THE END OF, OR DEAD WITHIN,	PATIENTS LIVING AT TIME OF SURVEY	PATIENTS DEAD AT TIME OF SURVEY
the 1st year	22% of all alive	80% of all dead
the 2nd year	32% of all alive	10% of all dead
the 3rd year	24% of all alive	1% of all dead
the 4th year	6% of all alive	4% of all dead
the 5th year	4% of all alive	1% of all dead
the 6th year	4% of all alive	0 of all dead
the 7th year	4% of all alive	2% of all dead
the 8th year	4% of all alive	

Of the 126 patients on whom we were able to obtain adequate data, 66 per cent were between the ages of 50 and 70 years (Table III). An additional 14 per cent were 70 years of age, or older. This agrees with the common conception that intraventricular block is associated with

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1. *Pharmaceuticals* (1998) 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, 500, 501, 502, 503, 504, 505, 506, 507, 508, 509, 510, 511, 512, 513, 514, 515, 516, 517, 518, 519, 520, 521, 522, 523, 524, 525, 526, 527, 528, 529, 530, 531, 532, 533, 534, 535, 536, 537, 538, 539, 540, 541, 542, 543, 544, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 567, 568, 569, 570, 571, 572, 573, 574, 575, 576, 577, 578, 579, 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 590, 591, 592, 593, 594, 595, 596, 597, 598, 599, 600, 601, 602, 603, 604, 605, 606, 607, 608, 609, 610, 611, 612, 613, 614, 615, 616, 617, 618, 619, 620, 621, 622, 623, 624, 625, 626, 627, 628, 629, 630, 631, 632, 633, 634, 635, 636, 637, 638, 639, 640, 641, 642, 643, 644, 645, 646, 647, 648, 649, 650, 651, 652, 653, 654, 655, 656, 657, 658, 659, 660, 661, 662, 663, 664, 665, 666, 667, 668, 669, 670, 671, 672, 673, 674, 675, 676, 677, 678, 679, 680, 681, 682, 683, 684, 685, 686, 687, 688, 689, 690, 691, 692, 693, 694, 695, 696, 697, 698, 699, 700, 701, 702, 703, 704, 705, 706, 707, 708, 709, 710, 711, 712, 713, 714, 715, 716, 717, 718, 719, 720, 721, 722, 723, 724, 725, 726, 727, 728, 729, 730, 731, 732, 733, 734, 735, 736, 737, 738, 739, 740, 741, 742, 743, 744, 745, 746, 747, 748, 749, 750, 751, 752, 753, 754, 755, 756, 757, 758, 759, 760, 761, 762, 763, 764, 765, 766, 767, 768, 769, 770, 771, 772, 773, 774, 775, 776, 777, 778, 779, 780, 781, 782, 783, 784, 785, 786, 787, 788, 789, 790, 791, 792, 793, 794, 795, 796, 797, 798, 799, 800, 801, 802, 803, 804, 805, 806, 807, 808, 809, 810, 811, 812, 813, 814, 815, 816, 817, 818, 819, 820, 821, 822, 823, 824, 825, 826, 827, 828, 829, 830, 831, 832, 833, 834, 835, 836, 837, 838, 839, 840, 841, 84

the 1990s, the number of people in the world who are under 15 years of age is expected to increase from 1.1 billion to 1.5 billion. The number of people aged 65 and over is expected to increase from 200 million to 400 million. The number of people aged 15 and over is expected to increase from 3.5 billion to 4.5 billion. The number of people aged 15 and over is expected to increase from 3.5 billion to 4.5 billion. The number of people aged 15 and over is expected to increase from 3.5 billion to 4.5 billion.

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TABLE IV

DISTRIBUTION OF PATIENTS WITH INTRAVENTRICULAR BLOCK ACCORDING TO TYPE AND ETIOLOGY

TYPE		PER CENT OF TOTAL CASES	NO. OF CASES	NO. WITH CORO- NARY ARTERY DISEASE OR HYPER- TENSION	NO. WITH SYPHILIS	NO. WITH RHEU- MATIC HEART	NO. WITH CONGEN- ITAL HEART DISEASE
<i>Common bundle branch type</i>	Dead at time of survey		40	37	2	1	0
	Alive at time of survey		27	26	1	0	0
	Both groups	53%	67	63	3	1	0
<i>Uncommon bundle branch type</i>	Dead at time of survey		9	7	0	2	0
	Alive at time of survey		4	0	1	2	1
	Both groups	10%	13	7	1	4	1
<i>Indeter- minate type</i>	Dead at time of survey		24	18	3	3	0
	Alive at time of survey		22	21	0	0	1
	Both groups	37%	46	39	3	3	1
Total			126	109	7	8	2
Per cent of total			100%	87%	5%	6%	2%
Per cent of each group alive at time of survey			40%	44%	30%	25%	100%
Per cent of each group dead at time of survey			60%	56%	70%	75%	0%

constitute 40 per cent of the entire series reviewed here, and 30 per cent of the entire series have already lived 2 to 8 years.

These findings have led us to the conclusion, which is in accord with that of Sampson and Nagle,⁵ that a high mortality rate occurs within the first year of the discovery of the lesion, but that the individuals who survive this dangerous period have a materially increased chance of living for many years. Two patients in this series who have already lived 8 years have minimal cardiac complaints. Bishop⁷ reported that one patient was living after 16 years. This study suggests that although permanent intraventricular block is evidence of serious involvement of the myocardium, unless other cardiac findings are present the lesion itself does not necessarily indicate an ominous prognosis.

We have analyzed the relation of the configuration of the electrocardiogram in intraventricular block to the prognosis. The greatest number of our patients (53 per cent) had the common bundle branch type of intraventricular block (Table IV). The next largest number (37 per cent) had one of the indeterminate types, and the uncommon bundle branch type was least common (10 per cent). The highest death rate occurred in the patients with the uncommon type (70 per cent),

although this group comprised only a small percentage of the entire series. The death rate of the patients with the common and indeterminate types of bundle branch block was similar, 59 and 53 per cent, respectively. It is thus noted that the higher death rate occurred in those patients who constituted only a small portion of the entire group (10 per cent), and the differences in death rate are probably not statistically significant. It would thus appear that the type of intraventricular block plays no significant role in the prognosis. There was also no correlation between the prognosis and the severity of the conduction defect as estimated by the QRS duration.

SUMMARY

1. We have recently conducted a follow-up study of a series of 126 patients whose electrocardiograms conformed to the criteria for the various varieties of intraventricular block, all showing a QRS duration of 0.11 second, or more.

2. The character of the underlying disease, rather than the presence or absence of intraventricular block, determines the prognosis, although the presence of intraventricular block carries with it a high mortality rate in the first year (particularly in the first three months).

3. We found a high fatality rate within a year of the discovery of the conduction lesion. Patients surviving this period have a materially better life expectancy. Apparently, a relatively benign type of intraventricular block occurs.

4. Neither the configuration of the electrocardiogram nor the duration of the QRS deflection is of prognostic significance.

ADDENDUM.—After our report was in press, another communication dealing with this subject was published by H. A. Freund and R. Sokolov: Bundle Branch Block, *Arch. Int. Med.* 63: 318, 1939. They reviewed 179 cases and came to essentially the same conclusions.

We wish to acknowledge our indebtedness to the physicians of the Hospital staff for kindly supplying us with information concerning their patients.

REFERENCES

1. Yater, Wallace M.: Pathogenesis of Bundle Branch Block, *Arch. Int. Med.* 62: 1, 1938.
2. Graybiel, A., and Sprague, H. B.: Bundle Branch Block, an Analysis of 395 Cases, *Am. J. M. Sc.* 185: 395, 1933.
3. King, J. T.: Bundle Branch Block: A Case Analysis With Especial Reference to Incidence and Prognosis, *Am. J. M. Sc.* 187: 189, 1934.
4. Wood, F. C., Jeffers, W. A., and Wolferth, C. C.: Follow-up Study of 64 Patients With a Right Bundle-Branch Conduction Defect, *AM. HEART J.* 10: 1056, 1935.
5. Sampson, J. J., and Nagle, O. E.: The Prognosis of Bundle-Branch Block and Other Intraventricular Conduction System Lesions, *Am. J. M. Sc.* 191: 88, 1936.
6. Bishop, L. F., Jr., and Carden, G. A., Jr.: The Prognosis of Bundle Branch Block, *AM. HEART J.* 17: 275, 1939.
7. Bishop, L. F., and Bishop, L. F., Jr.: Bundle Branch Block of Unusual Duration, *J. A. M. A.* 98: 398, 1932.
8. Katz, L. N., Landt, H., and Bohning, A.: The Delay in the Onset of Ejection of Left Ventricle in Bundle Branch Block, *AM. HEART J.* 10: 681, 1935.

THE EFFECT OF OXYGEN ON THE EXERCISE TOLERANCE OF PATIENTS WITH ANGINA PECTORIS

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IT HAS been shown that a relatively constant amount of work under standard conditions induces attacks of angina pectoris in a given patient. It is possible, therefore, to study the influence of various agents on this condition.^{1, 2, 3} The present communication describes the effect of breathing high concentrations of oxygen on the amount of work which patients with angina pectoris can do before developing pain.

METHODS

Seventeen patients with angina pectoris were studied in the present investigation. The exercise tolerance of each individual had been determined on at least fifty occasions during the preceding year. The tests were carried out in a room at constant temperature (45-55° F.), and consisted of having the patients repeatedly mount and descend a two-step staircase until an attack of angina developed.¹ The exercise was carried out at least one hour after a light breakfast; only one test was performed on any given day; and no medicament was taken by the patient for one week prior to the test.

The effect of oxygen was studied by having these individuals inhale pure, undiluted oxygen for ten minutes while standing at rest, and then having them exercise under the usual standard conditions while they continued to breathe oxygen. A series of Douglas bags connected to a stationary manifold served as a reservoir for the oxygen. Rubber tubing with an inside diameter of $\frac{3}{4}$ inch was led from this reservoir to a Krogh valve, in order to prevent rebreathing; the tubing and the valves were attached to the patient in such a way as to allow exercise with complete freedom. Control experiments were carried out in a manner which was identical except that the Douglas bags were filled with room air instead of oxygen. The patients were not aware of the composition of the gas breathed or its possible effect on their exercise tolerance.

RESULTS

Breathing room air from the Douglas bags did not increase the exercise tolerance of a single patient tested, and in several instances actually caused a decrease in the amount of work which could be done before developing angina (Table I).

Breathing oxygen from the Douglas bags enabled eleven of the seventeen patients to do considerably more work; four exercised until forced to stop because of fatigue without developing pain (Table I). Nine of these eleven patients were 39 to 53 years of age, and the remaining two were 57 and 58 years old. In seven patients, more than

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This investigation was aided by a grant from the DeLamar Mobile Research Fund.

Received for publication Dec. 12, 1938.

TABLE I

THE EFFECT OF BREATHING OXYGEN ON THE AMOUNT OF WORK WHICH CAN BE DONE BY PATIENTS WITH ANGINA PECTORIS

			EXERCISE TOLERANCE BREATHING ROOM AIR WITHOUT APPARATUS	EXERCISE TOLERANCE BREATHING ROOM AIR WITH APPARATUS	EXERCISE TOLERANCE BREATHING OXYGEN WITH APPARATUS	PER CENT TRIPS INCREASE
PATIENT	AGE	SEX	TRIPS	TRIPS	TRIPS	
Group A 11 Patients Benefited by Breathing Oxygen						
S.R.	57	M	33	35	61	85
H.B.	53	M	63	36	100*	59*
E.A.	58	M	28		41	46
P.R.	52	M	41	31	56	37
S.W.	39	M	37		50*	35*
M.F.	39	M	30		40	33
H.Shl.	53	M	46	48	60*	30*
B.K.	52	F	20	19	25	25
L.W.	51	M	42		52	24
M.R.	48	M	40		48	20
D.W.	53	F	37		44*	19*
Group B 6 Patients Not Benefited by Breathing Oxygen						
B.A.	51	M	45	35	47	4
M.L.	61	M	37	28	38	3
J.S.	57	M	32		32	0
R.S.	59	M	24		24	0
H.Shr.	61	M	30	22	29	-3
J.M.	62	M	30		26	-13

*No attack of angina precipitated; patient ceased exercise because of fatigue.

thirty-five trips were necessary to induce pain while breathing room air; the other four patients developed pain on less than thirty-five trips.

The remaining six of the seventeen patients were not able to do any more work while breathing oxygen. Only one of these patients was less than 53 years of age, and only two could perform more than thirty-five trips before developing angina.

COMMENT

It is evident that many patients with angina can do more work before developing pain if they breathe oxygen before and during exertion. Patients older than fifty-five and those who can do only a relatively small amount of work before developing pain are less likely to be benefited than those who are younger and have a relatively high exercise tolerance.

These findings are consistent with the anoxemia theory of angina pectoris. Richards and Barach⁴ have shown that breathing air enriched with oxygen during rest increases the oxygen content of the arterial blood. Hewlett, Barnett, and Lewis⁵ found that exercise results in a smaller rise of blood lactic acid if carried out while breathing oxygen-enriched air. Breathing oxygen both before and during exertion, therefore, tends to prevent myocardial anoxemia and its sequelae. These mechanisms, however, do not entirely compensate for a deficient coronary flow, for we find that the more elderly patients with a relatively

small tolerance to exercise, who presumably have a greater degree of coronary arteriosclerosis, are less likely to be benefited by oxygen. Furthermore, many of those patients who are helped by oxygen inhalation will develop pain if they exercise for sufficiently long periods of time.

Rothschild and Kissin⁶ have shown that attacks can be induced in some patients with angina by having them breathe room air depleted of its oxygen. The present investigation adds additional evidence in favor of the anoxemia theory, for it shows that attacks of angina can be prevented by preventing anoxemia.

REFERENCES

1. Riseman, J. E. F., and Stern, B.: A Standardized Exercise Tolerance Test for Patients with Angina Pectoris on Exertion, *Am. J. M. Sc.* 188: 646, 1934.
2. Riseman, J. E. F., and Brown, M. G.: Medicinal Treatment of Angina Pectoris, *Arch. Int. Med.* 60: 100, 1937.
3. Brown, M. G., and Riseman, J. E. F.: The Comparative Value of Purine Derivatives in the Treatment of Angina Pectoris, *J. A. M. A.* 109: 256, 1937.
4. Richards, D. W., and Barach, A. L.: Prolonged Residence in High Oxygen Atmosphere, *Quart. J. Med.* 3: 437, 1934.
5. Hewlett, A. W., Barnett, G. D., and Lewis, J. K.: The Effect of Breathing Oxygen Enriched Air During Exercise Upon Pulmonary Ventilation and Upon Lactic Acid Content of Blood and Urine, *J. Clin. Invest.* 3: 317, 1926.
6. Rothschild, M. A., and Kissin, M.: Production of the Anginal Syndrome by Induced General Anoxemia, *AM. HEART J.* 8: 729, 1933.

CARDIAC NEUROSIS ASSOCIATED WITH ORGANIC HEART DISEASE

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THE clinical picture presented by any patient with organic disease may be clouded by a superimposed neurosis.^{1, 2} Proper therapy and exact prognosis depend on recognition of, and attention to, this psychogenic component.

Although cases of cardiac neurosis associated with organic heart disease occur not infrequently, the proper diagnosis is often missed. The fault lies in the erroneous teaching that the diagnosis of neurosis is to be entertained only when organic disease has been excluded by negative physical, fluoroscopic, roentgenographic, and electrocardiographic findings, thus suggesting that combined neurotic and organic heart disease cannot exist. However, this is decidedly contrary to the vast experience of many clinicians.^{3, 4, 5, 6, 12}

An investigation was undertaken to determine what criteria were of value in the diagnosis of cardiac neurosis, particularly when associated with organic heart disease. One hundred seventy-two cardiac patients, the subject of this study, were classified into three groups: (a) those with organic heart disease, i.e., definite lesions, with orthodox symptoms, such as pain, dyspnea, orthopnea, etc.; (b) those with cardiac neurosis, i.e., precordial and other complaints, for which no organic basis could be demonstrated by present diagnostic methods; and (c) those with a cardiac neurosis associated with organic heart disease, i.e., definite cardiac lesions, with the same symptoms and signs as the patients in groups (a) and (b). Attention was directed to the predisposing and exciting factors of neurosis, its symptoms and its signs, and to a therapeutic test which aided in differentiating between the signs and symptoms due to neurosis and those caused by organic disease.

CONSTITUTIONAL AND PREDISPOSING FACTORS

Any person may develop a neurosis, individual differences being merely quantitative.^{8, 9, 10} The family history of several patients revealed a congenital predisposition. The hypersensitive, emotionally unstable individual with evidence of autonomic imbalance is most susceptible to neurosis, while the phlegmatic, calm patient succumbs only when the exciting factor is of unusual severity. Women at the time of the menopause are particularly prone to develop a neurosis.¹¹ The pres-

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Received for publication Nov. 11, 1938.

ence of organic heart disease seemed to be a factor in localizing the neurosis to the precordium, which is in accord with the psychiatric teaching that neurosis is often referred to a pathologic organ, i.e., the "organ inferiority" of Adler and "somatic compliance" of Freud.²¹ It is an axiom that "the cardiopath tends to become a neuropath."⁵¹

EXCITING CAUSES

The chief precipitating cause of cardiac neurosis in a person suffering from heart disease is usually the physician who exaggerates the severity of the disease, warns the patient of impending doom, and places long unwarranted restrictions on normal social and economic life. This was responsible for the majority of the cases in this series. Next in frequency was an anxiety neurosis initiated by abnormal precordial sensations due to premature beats, tachycardias, auricular flutter, and auricular fibrillation. In several cases, a compensation neurosis was precipitated by trauma to the left chest. Press reports of the sudden death of prominent men from coronary thrombosis occasionally caused acute anxiety in patients who had suffered from this disease. Other typical exciting causes were the death of a friend, relative, or fellow cardiac patient, legal difficulties, loss of position, disappointment in love, and business reverses.

SYMPTOMS

Pain was more frequently a presenting symptom in cardiac neurosis than in organic heart disease, except in cases of coronary thrombosis. One hundred per cent of those with coronary occlusion had abnormal precordial sensations. Forty-two per cent of those with organic disease, 80 per cent of those with organic heart disease and neurosis, and 96 per cent of those suffering only from cardiac neurosis had precordial distress (Table I).

TABLE I

PAIN, DEEP TENDERNESS, AND SUPERFICIAL HYPERALGESIA IN VARIOUS TYPES OF HEART DISEASE

TYPE	TOTAL	PAIN		PAIN AND DEEP TENDERNESS			PAIN, DEEP TENDERNESS, AND SUPERFICIAL HYPERALGESIA		
		No.	%	No.	A*	B*	No.	C*	D*
Organic heart disease	109	46	42	6	5	13	2	2	33
Org. heart disease with neurosis	25	20	80	15	60	75	14	56	93
Cardiac neurosis	25	24	96	20	80	83	20	80	100
Coronary occlusion									
Early	13	13	100	1	8	8	1	8	100
Convalescent	11	7	63	7	63	100	7	63	100

*A—Per cent of whole group.
B—Per cent of those with pain.
C—Per cent of whole group.
D—Per cent of those with pain and tenderness.

The description of the pain in the neurotic group appeared to be characteristic. It was described as sticking, stabbing, darting, lancinating, "pins and needles," or twinges most frequently localized beneath the left nipple and occasionally radiating to the angle of the left scapula. Some patients noted a residual soreness, which is rare in organic disease. Similar findings have been described by other authors.^{16, 19, 20} This type of pain, with its localization and radiation, could be recognized in cases of neurosis associated with organic disease as well as in patients with uncomplicated cardiac neurosis. It is known to be benign and to have no effect upon prognosis. No patient with only neurosis had substernal distress.

In the coronary group, the pain described was generally of two varieties. Acute pain was characterized as cramplike, squeezing, or pressing somewhere near the midline, with neither sternal nor epigastric tenderness or hyperalgesia. During convalescence, whenever pain was present, it was most often identical with that described in the "neurotic" group. Several patients who had been taught to test themselves for hyperalgesia reported inframammary twinges, "needles," etc., more frequently than their neighbors whose attention was not focused on the precordium. These sensations were of relatively short duration and were accompanied by tenderness and hyperalgesia. Psychic disturbances, such as that caused by the death of a neighbor, excitement during visiting hours, or anxiety the day before becoming ambulatory, occasionally increased the severity and duration of the distress. It was relieved successfully by the same therapy as was used in neurosis.

Weakness was a common complaint, the patient lying in bed seemingly exhausted even though there had been little or no expenditure of energy. The asthenia was always attributed by the patient to the "weak heart."

Sighing respiration was a concomitant of the asthenic state and is usually considered pathognomonic of neurosis.^{5, 23} This is occasionally misinterpreted as "shortness of breath" or "difficulty in breathing."

Insomnia was caused by involuntary mental activity due to a continuous uncontrolled flow of words and thought into consciousness. Neither pain nor dyspnea was responsible for insomnia.

ringing, pounding, or beating in the ears or temples, synchronous with the pulse, was a disturbing feature. Insomnia and ringing induced a vicious cycle.

Other common symptoms were fainting, faintness, dizziness, nervousness, irritability, and flushes.

SIGNS

Deep tenderness was elicited in the inframammary area in 5 per cent of patients having organic heart disease and in 80 per cent of those suffering from neurosis alone; 13 per cent of those in the organic group who suffered precordial pain also had deep tenderness, whereas 75 per cent of those with combined organic and neurotic heart disease and 83

per cent of the neurotics had deep tenderness associated with their pain. Tenderness was always localized to the inframammary area. It seldom occurs with pericarditis and is more often associated with nonorganic heart disease than with organic disease. Only one patient with acute coronary occlusion had inframammary tenderness associated with pain (Case 9). Inframammary tenderness, if not caused by extracardiac disease, is valuable evidence for the presence of cardiac neurosis.^{16, 22, 24}

Superficial hyperalgesia was demonstrated in less than 2 per cent of those with organic disease, whereas the incidence in cardiac neurosis was 68 per cent. Every patient with cardiac neurosis who had precordial pain and tenderness also had hyperalgesia, but this was true in only one-third of the patients with organic disease.

THERAPEUTIC TEST

An uncomplicated cardiac neurosis responds moderately well to simple forms of psychotherapy. However, it is quite difficult to convince patients who are cognizant of their organic disease that certain precordial sensations are of no significance.

The frequent finding of hyperalgesia suggested the injection intradermally of novocain into the affected area. It was surprising to note not only the immediate disappearance of hyperalgesia, tenderness, and pain, but also of symptoms not associated with the precordium which had been regarded as neurotic in origin. It was found unnecessary to inject the entire hyperalgesic area. The ethyl chloride spray, and, at times, saline intradermally and the oral administration of a red-colored placebo were found to be equally effective. Relief from symptoms varied from hours to months.

The procedure utilized Osler's³² three elements in the treatment of neurosis, i.e., a personality, various accessories, and suggestion. (1) The painful area was indicated by the patient. (2) Tenderness to finger pressure was demonstrated. (3) The hyperalgesic area was outlined with a pencil. The three areas invariably coincided. (4) The virtue of the medication to be used, its infallibility, and the immediate cure were stressed to the patient. (5) One or more small intradermal wheals were raised with 2 per cent novocain or saline in the area of hyperalgesia. (6) Immediately thereafter the disappearance of hyperalgesia over the wheals was demonstrated. Exploration of distant, noninjected, previously hyperalgesic areas showed them to be normal. (7) Tenderness and pain vanished. (8) Other symptoms, such as headache and dizziness, considered to be neurotic in origin, were frequently relieved.

The criteria for a positive therapeutic test are (1) immediate disappearance of pain, tenderness, and hyperalgesia, (2) relief of other symptoms not related to the precordium, (3) duration of relief for more than twenty-four hours, and (4) frequent recurrence of signs and symptoms due to psychic trauma or suggestion.

Although novocain has been injected intracutaneously occasionally to relieve visceral pain,^{33, 34, 35, 36} in most cases large quantities are used to block extensive areas of skin. In this series, organic pain was not relieved by the method described above. Moreover, in these cases criteria 2, 3, and 4 were not satisfied, making the therapeutic test negative.

REPORT OF CASES

Several cases are reported to demonstrate various features of cardiac neurosis associated with organic heart disease.

CASE 1.—Old coronary occlusion, cardiac neurosis. Constitutional factor: 54-year-old Irishman, unemployed, homeless. Precipitating factor: Six months previously, patient suffered a coronary thrombosis. He remained in the hospital for five months because of recurrent attacks of precordial pain which were assumed to be small recurrences, although there was no electrocardiographic or laboratory evidence.

Symptoms: Sticking pain beneath left nipple, inability to bend forward.

Signs: Inframammary tenderness and hyperalgesia.

Therapeutic test: Positive. All chest complaints disappeared immediately. Two days later when informed he would be discharged he developed intractable pain in the feet.

Comment.—Not every new precordial pain or ache in a patient with a known coronary occlusion is evidence of a new lesion. Physicians are fearful to assume, however, that it is benign, and many patients are invalided for a longer time than is necessary because of this fact.³⁷ A therapeutic test may be helpful in diagnosing superimposed neurosis.

CASE 2.—Recent coronary occlusion, nodal tachycardia, intractable shoulder pain, "brachial neuralgia," cardiac neurosis. Constitutional factor: 43-year-old, introspective, hypersensitive Italian, unemployed, in financial difficulties. Precipitating factor: Coronary occlusion, nodal tachycardia. Symptoms and signs: Patient had the typical history and electrocardiographic findings of infarction of the anterior wall of the left ventricle. One week after admission he began to complain of "pins and needles" localized to the inframammary region; tenderness and hyperalgesia were present.

Therapeutic test: He was relieved by a therapeutic test for ten days, when a paroxysm of nodal tachycardia began, associated with palpitation, "pins and needles," tenderness, and hyperalgesia. The palpitation disappeared with return of normal rhythm, but the other signs and symptoms remained. Pressure on the left brachial plexus increased the severity of the precordial pain. Suggestion, with the aid of a red-colored placebo, immediately relieved all symptoms and signs; brachial plexus pressure now had no effect on the pain. Two weeks following discharge he returned because of intractable pain in the left shoulder, with inability to abduct his arm. A localized area of pain, tenderness, and hyperalgesia was demonstrated at the tip of the left shoulder. Within one minute of the production of a small novocain wheal, all complaints had disappeared, and motion of the arm was complete in all directions.

Comment.—The coronary occlusion was the spark necessary to precipitate the neurosis to which this man was constitutionally susceptible. The abnormal precordial sensation of tachycardia caused a recurrence. Suggestion relieved both neurotic episodes. Several cases of intractable

pain in the shoulder and difficulty in abducting the arm have been seen following a coronary occlusion in which the radiation was to the affected shoulder.³⁸ The prompt response to psychotherapy makes one believe that some of these complaints are neurotic or hysterical in origin. These were not patients with the scalenus anticus syndrome.⁴⁷ Moreover, aggravation of precordial pain by brachial plexus pressure⁴⁸ is more frequently encountered in neurotics than in those with organic disease. Pressure on the top of the head (Case 6) or the lobe of the left ear will have the same effect in suggestible individuals. The pain may also be cured by increasing the pressure if suggestible patients (and neurotics are notoriously suggestible) are told that such a procedure will result in cure. "He cures most successfully in whom the people have the greatest confidence" (Galen³²).

CASE 3.—Rheumatic heart disease, traumatic or compensation cardiac neurosis.

Constitutional factor: 26-year-old, sheltered pharmacist, an only child, with a personal and family history of "nervousness."

Precipitating factor: Patient fell off a ladder, striking the left chest, two years previously, while employed as a drug clerk, and had been trying to obtain complete disability compensation since the accident. Recently he had heard that the verdict had been returned against him. The complaints became more severe.

Symptoms: "Pins and needles" in precordial region, weakness, flushes, sweats, insomnia, and nervousness.

Signs: Enlarged heart, mitral stenosis and insufficiency, aortic stenosis and insufficiency, regular sinus rhythm, functional classification IIA, inframammary tenderness and hyperalgesia.

Therapeutic test: Novocain relieved the complaints for three days. Symptoms recurred after his wife brought more bad tidings.

Comment.—Except for some diminution of his cardiac reserve, the patient had no definite subjective or objective distress until his accident. He attempted to prove that the accident two years previously caused new damage to his already diseased heart, giving as evidence the newly developed symptoms. However, these were in fact due to a superimposed cardiac neurosis. The rheumatic carditis was not responsible for the symptoms but may have caused the patient to focus his attention (and so localize his neurosis) to the precordium. The therapeutic test and the exacerbation of complaints by psychic trauma confirmed the clinical and legal impression of neurosis.

CASE 4.—Hypertensive and rheumatic heart disease, traumatic or compensation cardiac neurosis.

Constitutional factor: Thin, asthenic, unmarried, 40-year-old woman, in the menopause, emotionally unstable.

Precipitating factor: Patient fell on the sidewalk two years previously; a lawsuit was pending, and she was anxious over the outcome.

Symptoms: Dyspnea, orthopnea, sticking inframammary pain, extreme weakness, sighing respiration, flushes.

Signs: Enlarged heart, mitral stenosis and insufficiency, aortic stenosis and insufficiency, regular sinus rhythm, functional classification III, blood pressure 230/120, inframammary tenderness and hyperalgesia.

Therapeutic test: Two saline wheals relieved the patient of pain, subjective feeling of weakness, and sighing respiration, and decreased the number of flushes. It did not affect the dyspnea, orthopnea, basal rales, or size of the liver. Original complaints recurred after 10 days.

Comment.—This patient's heart was decompensated, yet there was definite evidence of an associated neurosis. Digitalis and the mercurials, of course, had no effect upon the latter. Therapy in compensation neurosis is generally unsuccessful until the litigation has ended.

CASE 5.—Rheumatic heart disease, cardiac neurosis.

Constitutional factor: Thin, pale, introspective, 24-year-old Italian girl.

Precipitating factor: Four years previously, during the course of a routine physical examination, a loud apical systolic murmur was heard. The physician told her that she had severe heart disease. She relinquished her position and since then had not ventured more than one-half mile from her home, fearing sudden death.

Symptoms: Palpitation, sighing respiration, weakness, insomnia.

Signs: Slightly enlarged heart, mitral stenosis and insufficiency, regular sinus rhythm, functional classification IIA, inframammary tenderness and hyperalgesia.

Therapeutic test: Two saline wheals successfully relieved her distress. Two months after discharge from the hospital there was still no recurrence; the patient was working and leading a normal existence.

Comment.—This neurosis was started and continued by a physician who measured the amount of cardiac damage and functional capacity by the loudness of a murmur. The patient had never had cardiac decompensation and the heart was only slightly enlarged, yet the physician interdicted all activity for months. This not only removed four years of usefulness from this girl's life but added an anxiety neurosis.

CASE 6.—Hypertensive heart disease, cardiac neurosis.

Constitutional factor: Obese, nervous Jew, 44 years of age, anxious about hypertension.

Precipitating factor: A physician told the patient that he had hypertension. He was warned not to eat meat or salt because, if he did, he might "get a clot on the heart."

Symptoms: Sticking pain over the left nipple, radiating down the left arm and up to the neck, not related to exertion, inability to completely abduct the left arm, dizziness, insomnia.

Signs: The heart was slightly enlarged, the blood pressure 160/110. Electrocardiograms revealed evidence of slight myocardial damage. Inframammary tenderness and hyperalgesia were present. Brachial plexus pressure and pressure on top of the head, on the left side, increased the precordial pain. It was observed that either a pinch of salt on his food or a forkful of meat would be followed immediately by complaints of increased pain, associated with exquisite precordial tenderness and hyperalgesia.

Therapeutic test: The ethyl chloride spray on one spot on the precordium relieved his distress and allowed immediate, complete abduction of the arm. He was slowly educated to the use of meat and salt.

Comment.—This patient with mild hypertension was completely disabled by the anxiety neurosis caused by the advice of his physician. "Too many persons have been made invalids for the rest of their lives through the discovery of questionable hypertension."³⁷

CASE 7.—No organic heart disease, cardiac neurosis.

Constitutional factor: 55-year-old, excitable, nervous Jew.

Precipitating factor: Following an attack of substernal pain three years earlier, electrocardiograms were taken and reported as showing evidence of marked coronary disease. His physician painted a dark prognostic picture, told the patient to give up his position, warned him about sudden death, and suggested that he remain at home for about six months.

Symptoms: Burning near the left nipple, radiating across the chest, occasionally "grabbing the throat," weakness, flushes, sighing respiration.

Signs: The heart was not enlarged. The blood pressure and electrocardiograms were normal. Inframammary tenderness and hyperalgesia were present.

Therapeutic test: Three intradermal novocain injections relieved the complaints immediately. He was told that the pain might recur about 10 A.M. the following day. At 10:30 A.M. he began to shout because of severe pain, which was quickly relieved by a saline injection.

Comment.—The patient was completely incapacitated mentally, economically, and socially by his neurosis. Incidentally, the electrocardiogram taken three years previously was obtained and found to be completely negative!

CASE 8.—Hypertensive heart disease, cardiac neurosis.

Constitutional factor: A 60-year-old German woman, anxious, worried.

Precipitating factor: The patient had been recently married to a man socially beneath her, who, after 6 months of married life, confessed that he had syphilis. On entrance she manifested marked syphilophobia.

Symptoms: Stabbing and burning over the left breast, weakness, flushes, sighing respiration, insomnia.

Signs: The heart was slightly enlarged, the blood pressure was 180/110, and the electrocardiogram showed some evidence of myocardial damage. Tenderness and hyperalgesia were present beneath the left nipple.

Therapeutic test: Positive.

Comment.—The patient had been seen by several physicians, all of whom attributed her symptoms to hypertensive heart disease. They had neglected to question her concerning her social and personal life. It is probable that many symptoms attributed to hypertension are really due to the neurosis which is often present in those individuals who are anxious about the level of their blood pressure.⁴⁹ The probable explanation for the dramatic relief of various symptoms by inert drugs and illogical operations is that suggestion eliminates the neurotic component from the clinical picture.

CASE 9.—Acute coronary occlusion, cardiac neurosis.

Constitutional factor: 56-year-old American woman, with a story of gastric neurosis and functional diarrhea since childhood; nervousness in family.

Precipitating factor: Coronary occlusion.

Symptoms: Twenty-four hours before admission, she was stricken with sudden, severe, vise-like, substernal pain, and went into shock. On arrival at the hospital her complaints were of sticking inframammary pain, weakness, and sighing respiration.

Signs: A pericardial friction rub was audible beneath the sternum. No tenderness or hyperalgesia was elicited over this area. The electrocardiogram revealed

evidence of infarction of the anterior wall of the left ventricle. Inframammary tenderness and hyperalgesia were present.

Therapeutic test: One intradermal novocain wheal relieved the pain, tenderness, and hyperalgesia for approximately 24 hours. The complaints recurred when a patient nearby suddenly became maniacal. The patient expired several days later, while asleep.

Comment.—This is the only case of acute coronary occlusion in which tenderness and hyperalgesia were found early. It illustrates White's²² statement that "a patient dying of coronary thrombosis may or may not have tenderness over the sternum or precordium; if he does it is not the heart disease that causes it but the excessive sensitiveness of the nervous system that is fundamentally responsible, the heart disease likewise being the precipitating factor." In our experience, pericarditis is infrequently associated with pain or tenderness. It was probably not responsible for this patient's later complaints. This case is presented to demonstrate that (1) cardiac neurosis may be associated with an acute coronary occlusion, and that, (2) just as discovery of an organic lesion does not rule out the presence of a cardiac neurosis, so the existence of a cardiac neurosis does not eliminate the possibility of an associated, severe, organic disease.

CASE 10.—Congenital heart disease, cardiac neurosis.

Constitutional factor: A 40-year-old German who had been committed to several mental institutions and was constitutionally defective.

Precipitating factor: While working as an orderly in a hospital, he had seen many cardiac patients die. He knew that he suffered from heart disease and was fearful of dying suddenly. Recently a member of his family had expired.

Symptoms: "Pins and needles" beneath the left nipple, weakness, sudden sweating, faintness, and insomnia.

Signs: Those of coarctation of the aorta. Tenderness and inframammary hyperalgesia were present.

Therapeutic test: Positive. Complaints recurred whenever a death occurred on the ward.

Comment.—This fear of death, particularly in heart patients, brings up the question of the advisability of segregating all patients with coronary occlusion in one room or ward. The sudden death of one of these patients must "strike terror in the hearts" of the others, who see this as evidence that their own fate is impending. The slightest precordial sensation would be expected, then, to cause panic in these individuals.

CASE 11.—Congenital heart disease, cardiac neurosis.

Constitutional factor: A 30-year-old American woman, obese, pregnant for two months.

Precipitating factor: She had been warned by her physician not to become pregnant because she had heart disease. Symptoms began when she discovered that she was pregnant.

Symptoms: Precordial sticking and burning, weakness, dizziness, faintness.

Signs: There was audible a machinery-like murmur at the pulmonic and left sternal regions. A systolic thrill (possibly caused by patency of the ductus) was

palpable over the upper precordium. Tenderness was present over the left breast, and hyperalgesia was limited by the midline to the entire left side of the body.

Therapeutic test: Novocain immediately relieved the pain and tenderness but caused a complete left hemianesthesia. The patient left the hospital before investigation could be completed.

Comment.—Autosuggestion was so marked in this case that the demonstration of anesthesia over the novocain wheal was sufficient to suggest complete unilateral anesthesia.

CASE 12.—No organic disease, abdominal neurosis, induced cardiac neurosis.

Constitutional factor: Obese, nervous, Jewish woman, in the menopause.

Precipitating factor: Patient's son had been sentenced to several months in jail for petty larceny six days before patient was admitted to the hospital.

Symptoms: Pain in right upper quadrant, anorexia, aerophagia, sighing respiration, insomnia, and flushes, all of recent occurrence.

Signs: Slight tenderness in right upper quadrant, hyperalgesia limited to tender area.

Therapeutic test and comment.—This case is presented to demonstrate the role played by heterosuggestion in the etiology of all neurosis, particularly cardiac neurosis. The patient had no signs or symptoms referable to the heart, either in the past or present. Each day for five successive days her heart was examined, and tenderness and hyperalgesia were sought but not found. No comments were made, nor did anything in the examiner's manner or expression suggest the presence of disease. On the sixth day, after listening intently over the precordium, the examiner appeared worried, and asked the patient repeatedly if she was sure there was nothing wrong with her heart, and if she had not felt any pain over the left breast. The patient answered in the negative, but two hours later the intern was called to see her in an attack of severe inframammary pain, sticking in character. Tenderness and hyperalgesia were elicited. A therapeutic test relieved not only her precordial distress, but also the right upper quadrant pain which had been the original cause for her admission to the hospital. It is probable that many cases of cardiac neurosis are precipitated in suggestible individuals by such suggestion by physicians. Incidentally, Morley³⁰ states that hyperalgesia is frequently elicited over the abdomens of neurotic patients in whom exploratory laparotomy reveals no evidence of disease.

DISCUSSION

All neurosis is caused by, or is the result of, hetero- and autosuggestion.³¹ The latter^{28, 30} is probably responsible for the pain, tenderness, and hyperalgesia found in cardiac neurosis. Thirty patients convalescing from other diseases were asked, (1) If you had heart disease where would you feel the pain? (2) Would finger pressure on one side hurt more than on the other? Where? (3) Would a pin prick be felt more on one side than the other? Where? Twenty-seven patients localized the pain near the left nipple, 25 believed tenderness would be present in

that area, and 23 expected hyperalgesia in the same region. Since the majority of laymen believe this triad to be associated with heart disease, one would expect it to be elicited in autosuggestible neurotics who believe they are so afflicted. It is the characteristic clinical finding in cardiac neurosis.

The small amount of novocain used in these investigations acts by suggestion, since relief was also obtained by other simple procedures directed to the affected area. The demonstration of the loss of hyperalgesia (as prophesied by the physician) probably has marked autosuggestive power. Moreover, the immediate, complete relief of symptoms, regarded with intense anxiety, by so simple a method helps to convince the patients of their unimportance. This use of novocain in hysterical hyperalgesia is a counterpart of Hurst's²⁹ therapy of hysterical anesthesia with faradic stimulation.

CONCLUSIONS

(1) Cardiac neurosis is a distinct entity with characteristic findings which are recognizable even in the presence of organic heart disease. The criteria for a diagnosis of this condition are (A) an inherited or acquired predisposition to neurosis, (B) a definite precipitating factor, (C) symptoms such as inframammary pain, weakness, sighing respiration, insomnia, dizziness, ringing in the ears, nervousness, and irritability, (D) inframammary tenderness and hyperalgesia, and (E) relief by simple procedures such as the therapeutic test described, namely, intradermal injection of small quantities of 2 per cent novocain together with suitable suggestion, the latter being the more important factor.

(2) Individuals suffering from organic heart disease may have symptoms and signs similar to the above which can be proved to be of neurotic origin.

(3) When precordial pain is accompanied by superficial hyperalgesia and deep tenderness, it is more likely to be of neurotic than organic origin.

(4) The findings in a group of 172 patients admitted to the hospital with a diagnosis of heart disease are described, and cases are reported to illustrate some of the features of combined organic and neurotic heart disease.

REFERENCES

1. Alvarez, W. C.: Ways of Improving Gastroenterology, *Rev. Gastroenterol.* 4: 160, 1937.
2. Wechsler, I. S.: Differential Diagnosis of Neurosis from Organic Disease, *Med. Clin. North America* 21: 1847, 1937.
3. Herrich, J. B.: *Forschheimer's Therapeutics of Internal Diseases* 5: 316, 1925.
4. White, P. D.: *Nelson's Looseleaf Medicine* 4: 637.
5. Craig, H. R., and White, P. D.: Etiology and Symptomatology of Neurocirculatory Asthenia, *Arch. Int. Med.* 53: 633, 1934.
6. Edwards, J. C., and White, P. D.: A Note on the Incidence of Neurocirculatory Asthenia With and Without Organic Heart Disease, *New England J. Med.* 211: 53, 1934.

7. Criteria for the Classification and Diagnosis of Heart Disease: N. Y. Tuberculosis and Health Assoc., New York, 1932, Little and Ives, p. 13.
8. Hurst, A. F.: The Constitutional Factor In Disease, London, 1927, Paul T. Trubner and Co.
9. Draper, G.: Human Constitution, Philadelphia, 1924, W. B. Saunders Co.
10. Draper, G., Dunn, H. T., and Seegal, D.: Studies in Human Constitution, Am. J. M. Sc. 169: 322, 1925.
11. Novak, E.: The Menopause and Its Management, J. A. M. A. 110: 619, 1938.
12. Conner, L. A.: Psychic Factor in Cardiac Disorders, J. A. M. A. 94: 447, 1930.
13. Yaskin, J. D.: Cardiac Psychosis and Neurosis, AM. HEART J. 12: 536, 1936.
14. Viko, L. I.: Cardiac Neurosis Associated with Rheumatic Valvular Heart Disease, AM. HEART J. 1: 527, 1926.
15. Bleuler, E., and Brill, A. A.: Textbook of Psychiatry, New York, 1930, The Macmillan Co.
16. Baker, D. M.: Left Inframammary Pain, Lancet 1: 1280, 1930.
17. Kilgore, E. S.: Angina Pectoris and Pseudoangina, J. A. M. A. 87: 455, 1926.
18. Kilgore, E. S.: The Nervous Heart, AM. HEART J. 5: 9, 1929.
19. Levy, H., and Boas, E. P.: Coronary Artery Disease in Women, J. A. M. A. 107: 97, 1936.
20. Parkinson, J.: Left Scapular Pain and Tenderness in Heart Disease, Lancet 1: 550, 1919.
21. Wittkewer, E.: Psychological Factors in Cardiac Pain, Lancet 2: 665, 1937.
22. White, P. D.: Precordial Pain and Tenderness, New England J. Med. 206: 1283, 1932.
23. White, P. D., and Hahn, R. G.: The Symptoms of Sighing in Cardiovascular Diagnosis, Am. J. M. Sc. 177: 179, 1929.
24. Kellogg, F., and White, P. D.: The Clinical Significance of Precordial Tenderness, New England J. Med. 206: 659, 1932.
25. Mackenzie, J.: Diseases of the Heart, London, 1918, H. Frowde, Hodder & Stoughton.
26. Mackenzie, J.: Angina Pectoris, London, 1923, H. Frowde, Hodder & Stoughton.
27. Eppinger, E. C., and Levine, S. A.: Angina Pectoris, Arch. Int. Med. 53: 120, 1934.
28. Hurst, A. F.: Medical Diseases of the War, London, 1918, Edward Arnold & Co.
29. Hurst, A. F.: The Psychology of the Special Senses and Their Functional Disorders, Croonian Lectures, London, 1920, H. Frowde.
30. Morley, J.: Abdominal Pain, New York, 1931, William Wood & Co., p. 118.
31. Wechsler, I. S.: Textbook of Clinical Neurology, Philadelphia, 1936, W. B. Saunders Co., p. 695.
32. Osler, W.: Principles and Practice of Medicine, New York, 1917, D. Appleton-Century Co., p. 1115.
33. Weiss, S., and Davis, D.: The Significance of the Afferent Impulses from the Skin in the Mechanism of Visceral Pain, Am. J. M. Sc. 176: 517, 1928.
34. Rudolf, R. D., and Smith, A. G.: Observations on Visceral Pain, Am. J. M. Sc. 180: 558, 1930.
35. Morley, J.: The Significance of the Afferent Impulses from the Skin in the Mechanism of Abdominal Pain, Lancet 2: 1240, 1929.
36. Lemaire, A.: La Perception des Douleurs Viscerales, Rev. med. de Louvain 6: 81, 1926.
37. Crain, R. B., and Missal, M. E.: The Employee with Heart Disease, J. A. M. A. 110: 1, 1938. Discussion by W. D. Stroud and E. P. Boas.
38. Edeiken, J., and Wolferth, C. C.: Persistent Pain in the Shoulder Region Following Myocardial Infarction, Am. J. M. Sc. 191: 201, 1936.
39. Menninger, K. A., and Menninger, W. C.: Psychoanalytic Observation in Cardiac Disorders, Am. J. M. Sc. 191: 201, 1936.
40. Libman, E.: Etiology of Subacute Infective Endocarditis, Am. J. M. Sc. 140: 516, 1910.
41. Libman, E.: Clinical Features of Subacute Streptococcus Endocarditis, M. Clin. North America 7: 117, 1918.
42. Pearson, R. S. B.: Psychoneurosis in Hospital Practice, Lancet 1: 451, 1938.
43. White, P. D.: Functional Disorders of the Heart, AM. HEART J. 1: 527, 1926.
44. Kerr, W. J., Dalton, J. W., and Gliebe, P. A.: Some Physical Phenomena Associated with Anxiety States, Ann. Int. Med. 11: 961, 1937.
45. Flynn, J. M.: Somatic Phenomena in Psychoneurosis, Am. J. M. Sc. 193: 548, 1937.

46. Meakins, J. C.: The Practice of Medicine, St. Louis, 1936, The C. V. Mosby Co., p. 468.
47. Reid, W. D.: Pressure on the Brachial Plexus Causing Simulation of Coronary Disease, J. A. M. A. 110: 1724, 1938.
48. Boas, E. P., and Levy, H.: Extra-Cardiac Determinants of the Site and Radiation of Pain in Angina Pectoris with Special Reference to Shoulder Pain, AM. HEART J. 14: 540, 1937.
49. Ayman, D., and Pratt, H. H.: Nature of the Symptoms Associated with Essential Hypertension, Arch. Int. Med. 47: 675, 1931.
50. Romberg, M. H.: A Manual of the Nervous Diseases of Men, London Sydenham Society 1: 9, 1853.
51. Lindsey, J. A.: Medical Axioms, Aphorisms and Clinical Memoranda, London, 1923, H. K. Lewis & Co., p. 54.

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ACUTE ENDOCARDITIS IN WILD ANIMALS, WITH ESPECIAL REFERENCE TO THE OPOSSUM

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UNDERSTANDING of acute endocarditis, particularly of the valves, may be widened by a knowledge of its occurrence in wild animals. In man, this pathologic process is commonly associated with rheumatism, or follows upon a flagrant acute infection. That rheumatism occurs spontaneously in lower animals remains to be proved, while acute fulminating infections are common and end fatally with great rapidity. Here follows an account of acute endocarditis as seen in the autopsy service at the Zoological Gardens at Philadelphia over a period of thirty years. Such evidence as can be adduced would certainly blame cocci as the principal cause, but a few unusual bacterial varieties are also represented. Unfortunately, the facilities for thorough bacteriologic study were not regularly available.

CARNIVORA

Felidae.—Lion 1809, 91 months' exhibit, had been in poor health for many days before death, which resulted from acute vegetative and ulcerative mitral and aortic valvulitis from which the anaerobic *B. Afanassieffi* (Migula-Chester) was isolated. Several embolic lesions were found, notably a large infarct in the spleen. (See Ostrich 6222.)

Canidae.—Fox 5765, 13 months' exhibit, with no history of illness. There was a subacute and recent mitral valvulitis, and pneumonia.

MARSUPIALIA

Dasyuridae.—Tasmanian Devil 6017, 50 months' exhibit. Suffered for some time with an abscess in mandible, probably of streptothrichal origin, ending as an acute infection comparable, in lesions, to canine distemper. The mitral valve only had acute vegetations.

Didelphiidae.—Opossum—American variety throughout.

1799, 17 days' exhibit, presented evidences of an acute general infection of severe grade, including embolic foci such as abscesses; endocarditis involving all valves, the aortic particularly.

2085, 1 month's exhibit, never in good condition; acutely ill for several days before death, apparently with an infection like canine distemper. Mitral and aortic valves showed vegetations from which, however, no embolism had arisen.

2115, 2 months' exhibit. Belonged to same batch as 2085 and presented almost exactly the same lesions.

2348, 9 months' exhibit. No history. Acute general infection, pneumonic consolidations, and mural endocarditis.

From the Penrose Research Laboratory, Philadelphia Zoological Society.
Received for publication Dec. 21, 1938.

2519, 1 month's exhibit. No history. Acute general infection due to the pneumococcus, with valvulitis of all valves on the left side of the heart, passive congestion of the liver, and embolic foci in the kidneys.

2544, 16 months' exhibit. Very extensive, severe, and rapid infection, giving rise to pancarditis and stenosis and incompetency of valves (record not thorough).

2550, 1 month's exhibit. Acute general infection seriously affecting mitral and aortic valves and giving embolic phenomena.

9526, 1 month's exhibit. Acute general infection due to staphylococcus, with mitral lesions and many embolic abscesses.

9508, 5 months' exhibit. A general infection, probably originating in a mucopurulent bronchitis. The mitral valve showed vegetative lesions and there were acute splenic tumor and a small renal abscess.

10,159, 4 months' exhibit. No history, protocol not thorough. Mitral valvulitis, acute splenitis, abscess in kidney, bloodstained urine in bladder.

10,270, 4 months' exhibit. Injury to leg, probably with infection. Decomposed at autopsy, vegetations on mitral valve only.

11,061, 2 months' exhibit. No history, protocol not thorough, but body probably the same, including mitral valve, as 10,270.

11,011. Time on exhibit not certain, no history. Infection of pyemic type, emboli in spleen, kidney, and liver, with mitral vegetations.

The disproportionate number of opossums (all *Didelphis m. virginiana*) may be a result of the fact that more of these animals (271) have come to autopsy than any other. It is worth recording, however, that among 57 other opossums and 154 Australian marsupials, 93 rhesus macaque monkeys, 83 raccoons, 83 porcupines, and several large orders there were no cases of acute valvulitis. Opossums are never bought by the Zoo; they are usually donated by friends, commonly only with the story that they were found on the farm or free in the country. These animals adjust themselves poorly to captive conditions in a menagerie, the length of life being short and the death rate high. Younger opossums, and especially very young ones with the mother, show much osseous degeneration of the rickets type. There is a suggestion in these figures that opossums have a low endocardial resistance.

PASSERIFORMES

Icteridae.—Rice Grackle, 186 months' exhibit. Had been in poor condition for some time, probably because of leg arthritis and pectoral myositis. There were acute endoaortitis and endocarditis of the seromuscular fold between the right auricle and ventricle.

ACCIPITRIFORMES

Falconidae.—Buzzard 3606, 43 months' exhibit. Had poor feet for some time before death, but otherwise in good condition. Apparently nothing was wrong with the legs and feet, for the protocol fails to mention them. Thrombotic mitral valvulitis with splenic tumor.

Buzzard 3870, 2 months' exhibit. No history. Vegetative mitral valvulitis, with emboli in spleen and acute hepatitis.

Eagle 10,566, 5 months' exhibit. Gasping and not eating for 6 days ante mortem. Wound (from fighting?) in beak. Flat, not covered, not ulcerated, vegetations on seromuscular fold between right-sided chambers of the heart. Abscesses in myocardium, lung, and abdominal space. Staphylococcus cultured from heart valve.

Eagle 6827, 54 months' exhibit. Cellulitis of legs for a week ante mortem, due to *Staphylococcus aureus*. Acute general infection seemed to arise from this, leading to mitral valvulitis and acute splenitis.

Eagle 2447, exhibit (?). Mural endocarditis around pulmonary base and aortic conus.

STRIGIFORMES

Strigidae.—Owl 11,212. Injury in axillary region. No history. Thrombotic valvulitis of aortic and nearest mitral leaflet, extending into the aorta and left brachiocephalic vessel.

ANSERIFORMES

Anatidae.—Falcated Duck, 3566, 10 days' exhibit. Recent cauliflower vegetations on mitral valve, with acute splenitis.

Mallard Duck, 3599, (domestic ?) 5 days' exhibit. A recent, acute thrombotic mitral valvulitis, with necrotizing embolic lesions in spleen.

Duck, 5653, 49 months' exhibit. Recent myocarditis, and valvulitis of mitral and aortic leaflets, with embolism of spleen and kidney.

Duck, 9623, 11 years' exhibit. Recent injury to head. Thrombotic valvulitis of mitral valve, extending as a prolongation, not implantation, through aortic orifice and obstructing it.

Teal, 10,209, 8 years' exhibit. Crippled two months. Vegetation on pulmonary tricuspid valve, without obstruction, extension, or emboli.

Goose, 11,675, 23 years' exhibit. Injury to foot followed by local infection. General condition not poor at autopsy. Thrombotic valvulitis, posterior aortic cusp; plugging embolus in second left renal artery. Chronic focal nephritis; arteriosclerosis; thyroiditis. *Staphylococcus* forms in smear from valve.

Chinese Goose, 12,694. No history, 9 months' exhibit. Granulomas of feet that became infected. *Streptococcus* of human type in foot and in vegetations on mitral and aortic valves. Acute diffuse hepatitis; acute focal and diffuse nephritis, both interstitial and parenchymatous; some scattered glomerulitis; mild acute degenerative and infiltrative myocarditis; vegetative and ulcerative valvulitis. This streptococcus killed a guinea pig in 7 days when given intraperitoneally in a dose of 1 c.c. of 24-hour meat infusion broth culture per 1000 gm. of pig weight. It had exudative pneumonitis and pleuritis. When reisolated the coccus was, with one exception, the same as stock controlled strain; it had become hemolytic. A rat, mouse, rabbit, pigeon, and two geese remained alive 4 months after injections of comparable doses. No distinct lesions were discovered when they were killed.

Goose, 12,387, 20 years' exhibit. Well until 2 months before death, when it was found incoordinate. Very early granulations along closure line of pulmonary valve, which showed, on smear, streptococci in short chains.

Swan, 9529, 2 months' exhibit. Chronic amyloid disease of liver, kidney, and spleen, with pyelitis. Purulent arthritis of left leg. Came to menagerie lame. Recent small vegetations on mitral valve.

PHOENICOPTERIFORMES

Phoenicopteridae.—Flamingo, 10,573, 6 years' exhibit. Recently developed acute arthritis of both feet, probably from an old lesion. Early pulmonary tuberculosis (arthritis also tuberculous?). On closure line of mitral valve there were small, gray, friable vegetations containing staphylococci. Myocardial degeneration; embolic abscesses in kidney.

ARDEIFORMES

Ardeidae.—Heron 7819, 5 months' exhibit. No history. Acute malignant valvulitis, superimposed on fibrous, thickened, and calcareous valves. Acute enteritis and nephritis.

Plegadidae.—Ibis, 9677, 10 years' exhibit. No history. Death from acute enteritis. Recent mural endocarditis on wall of left ventricle.

Ibis, 11,404, 26 years' exhibit. No history. Chronic salpingitis and arteriosclerosis. Recent vegetative endocarditis on mitral and aortic valves. *Staphylococcus* found in the smear. Embolic foci in kidney, and acutely hyperplastic spleen.

BALEARICIFORMES

Balearicidae.—Crane, 2 months' exhibit. Never did well, probably because of pedal fibromas. Osteomalacia and tuberculosis of lung. One recent vegetation on aortic valve.

CHARADRIIFORMES

Burhinidae.—Thicknee, 9963, 13 years' exhibit. Lame in left leg from purulent pedal arthritis. Vegetation on pulmonary tricuspid that extended along artery to lungs. Other organs in early decomposition, but seemed otherwise normal.

Charadriidae.—Oyster Catcher, 6158, 5 months' exhibit. Scaly legs and feet for months before death. Cardiac lesion only important one found. Mitral (aortic leaflet) seat of recent vegetation running into auricle. Protocol states that *Staphylococcus aureus* was isolated, but note also indicates that Gram-negative cocci in staphylococcus groups and in short chains were seen in valves. No emboli.

CASUARIIFORMES

Casuaridae.—Cassowary, 5227, 8 years' exhibit. No history. Protocol not clear. Vegetations on all valves.

Cassowary, 6590, 69 months' exhibit. No history. Despite a very advanced general infection, body was in good state of strength and preservation. Most important acute and advancing lesion not certain, but endocardial changes very marked. Bacteriologic culture overgrown by mould. Auriculoventricular fold of right side and mitral leaves showed vegetative endocarditis of productive type.

STRUTHIONIFORMES

Struthionidae.—Ostrich, 6222, 34 months' exhibit. Afanassiew's bacillus (*Migula-Chester*) and colon bacillus isolated from heart blood and vegetation. Vegetative and ulcerative lesions, with stenosis, on mitral and aortic valves. Splenitis with one abscess; parenchymatous nephritis; acute necrotizing enteritis. (See Lion 1809.)

Ostrich, 7319, 175 months' exhibit. Out of condition 1 week. Chronic enteritis and acute pancreatitis and splenitis. Recent mural and valvular endocarditis. *Staphylococcus aureus* cultured from heart and spleen.

CARNIVORA	<i>Felidae</i>	Lion	1
	<i>Canidae</i>	Fox	1
MARSUPIALIA	<i>Dasyuridae</i>	Devil	1
	<i>Didelphiidae</i>	Opossum	13
			<hr/> 16
PASSERIFORMES	<i>Icteridae</i>	Grackle	1
ACCIPITERIFORMES	<i>Falconidae</i>	Buzzard and Eagle	5
STRIGIFORMES	<i>Strigidae</i>	Owl	1
ANSERIFORMES	<i>Anatidae</i>	Duck	5
		Goose	3
		Swan	1
PHOENICOPTERIFORMES	<i>Phoenicopteridae</i>	Flamingo	1
ARDEIFORMES	<i>Ardeidae</i>	Heron	1
	<i>Plegadidae</i>	Ibis	2
BALEARICIFORMES	<i>Balearicidae</i>	Crane	1
CHARADRIIFORMES	<i>Burhinidae</i>	Thicknee	1
	<i>Charadriidae</i>	Oyster Catcher	1
CASUARIIFORMES	<i>Casuaridae</i>	Cassowary	2
STRUTHIONIFORMES	<i>Struthionidae</i>	Ostrich	2
			<hr/> 27

Analysis of the pathologic forms shows predominance of the vegetative and thrombotic processes, ulceration being rare. Extension to the aortic and pulmonary vessels occurs almost exclusively in birds. Embolic secondary lesions were, as in man, chiefly in the kidneys and spleen, as infarcts, abscesses, and glomerular lesions. Distinct embolic lesions were seen in 8 of 16 mammalian cases, and in 7 of 27 avian cases.

The endocardial distribution of lesions was as follows:

Aortic valves	-	-	-	-	-	7 of 16 mammals	-	-	-	-	-	6 of 27 birds
Mitral valves	-	-	-	-	-	15 of 16 mammals	-	-	-	-	-	15 of 27 birds
Pulmonary valves	-	-	-	-	-	1 of 16 mammals	-	-	-	-	-	3 of 27 birds
Mural valves	-	-	-	-	-	1 of 16 mammals	-	-	-	-	-	2 of 27 birds
Right tricuspid	-	-	-	-	-	0 of 16 mammals	-	-	-	-	-	
Seromuscular right												
auriculoventricular fold	-	-	-	-	-		-	-	-	-	-	3 of 27 birds

The medical history may be of some significance in attempting to explain the origin of the endocarditis. Recent injury was noted in the history of 3 birds and 2 mammals. Injury of somewhat longer duration, pedal fibromas, and arthritis were recorded for 1 mammal and 10 birds. Several of the opossums had wounds of the feet. Acute infection (disseminated type) was seen in 3 mammals, and chronic infection, usually an unhealed wound or slowly spreading cellulitis, in 1 mammal and 3 birds.

It is not the purpose of this article to imply that these cases represent the exact incidence of endocarditis in wild animals, but to place on record what was found in the performance of some 13,000 autopsies. The high opossum incidence has been mentioned and partly explained, but the flagrancy of the lesions and the briefness of the period during which these animals were on exhibition have not been emphasized. Every endocarditic lesion adequately described was prominently vegetative, more so than in most of the other animals, notably the birds. Four opossums had been on exhibition 1 month or less, suggesting that the process antedated capture, or began soon thereafter, upon coming in contact with unusual bacteria, and probably indicating a high vulnerability of the endocardium. Two others had an exhibition time of 2 months. Only five other animals in this series have short exhibition times, namely, a buzzard, 2 ducks, a swan, and a crane. The others lived longer periods. an ibis even 26 years.

Though no claim concerning incidence is made, even for the opossum, it is well to record that the following animals were autopsied without finding endocarditis:

Primates 820, Rodentia 500, Artiodactyla 475, Psittaciformes 1300, and smaller numbers belonging to many other orders.

THE EFFECTS OF WHOLE BILE AND BILE SALTS ON THE PERFUSED HEART

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IN CLINICAL and experimental work one frequently encounters cases in which the toxicity of bile is manifested. In addition to other symptoms, bradycardia is common in patients with severe icterus. These general observations led us to undertake some investigations on the perfused mammalian heart which may contribute to a better understanding of the mechanism by which whole bile and bile salts affect the heart. These experiments enabled us, not only to watch the heart while it was manifesting the various changes that occurred when whole bile or bile salts were added to the perfusate, but also to take graphic records of the amplitude, rate, and rhythm of the cardiac contractions and of the disturbances appearing under the influence of the bile constituents. We found that whole bile from the gall bladder and commercial preparations of bile salts, when used in the perfusate, produce definite changes in the amplitude, rate, and rhythm of the contractions of the isolated heart.

Horrall's¹ review gives an excellent survey of the literature dealing with the toxicity of bile. He very clearly demonstrates the diversity of the opinions and of the results given by different workers. One of the constant autopsy findings of Bunting and Brown² was a pale, dilated, hyalinized, and necrosed myocardium, to which they attributed the death of their rabbits within twenty-four hours after the intraperitoneal injection of bile. Battaccano and Vasiliu³ attributed the hypotension produced by intravenous injections of sodium glycocholate to the direct toxic effect on the heart. Emerson⁴ produced a fall in blood pressure, arrhythmia, and sometimes cessation of cardiac activity by intravenous injection of whole bile or bile salts into dogs. He found sodium glycocholate to be more toxic than sodium taurocholate. Horrall and Carlson⁵ concluded that bile salts act on the vagus endings, and also directly on the heart muscle through the coronary circulation. Regan and Horrall⁶ observed a fall in blood pressure as a result of intravenous injection of sodium glycocholate into dogs. Still⁷ showed that small doses of bile acids, slowly administered intravenously, produce a slight rise in blood pressure, while large amounts produce a marked fall. He expressed the opinion that the effects of bile acids are "due to their being general protoplasmic poisons." Ries and Still⁸ concluded from their observations on dogs that bile salts in small doses cause an increase in the ir-

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Received for publication Jan. 26, 1939.

ritability of the vagal endings and that large doses tend to cause block of the same endings. The changes of pulse rate in cases of obstructive jaundice were attributed to the effects of bile salts on the endings of the vagus nerve. Meltzer and Salant,⁹ in their work on etherized rabbits, confirmed Still's observations of the fall in blood pressure, and stated that bile inhibits the activity of the heart. Buchbinder¹⁰ attributed the bradycardia produced in his experimentally jaundiced puppies to a reflex through the vagus. Baruk and Camus¹¹ injected human bile into various experimental animals and concluded that the symptoms produced could be attributed to bulbar intoxication. They observed that bile salts have a greater paralytic action than whole bile.

The explanations of the toxic effects of bile constituents given by the various investigators differ so widely because of the presence of a number of mechanisms in the intact animal which render the situation equivocal. Among the possible causes for the controversy over the effect of bile constituents on the heart may be the difficulty of controlling the various factors operating in the intact animal.

METHOD

In order to avoid some of the uncontrollable factors, our investigations were performed on the isolated hearts of rabbits. The rabbits were etherized and bled through the aorta and inferior vena cava into a 2 per cent sodium citrate solution. The heart was removed, washed in warm Ringer-Locke solution, and perfused according to the usual procedure. The perfusate was made of oxygenated Ringer-Locke solution in triple-distilled water, according to the formula given by Bayliss,¹² and was kept at a constant temperature of 38° C. throughout the experiment. Oxygenation was produced by constantly bubbling oxygen through the reservoir containing the perfusate. The only interruption in the whole setup was the shifting from one Ringer-Locke perfusate to another to which a known quantity of whole bile or bile salt had been added. Whole bile was procured from the gall bladder by aspiration, and filtered before use. We used human, rabbit, and dog bile. The bile salts used were commercial preparations of sodium taurocholate (Merck) and sodium glycocholate (Mallinckrodt). In the experiments in which red blood corpuscles were used, the citrated blood was centrifuged and the red cells were washed several times with Ringer's solution before they were added to the perfusate. The contractions of the heart were recorded on a revolving kymograph by means of a lever connected to the apex. To prevent the passage of any particles that might interfere with the coronary circulation, the perfusate was filtered through glass wool before it reached the heart.

In some experiments, instead of introducing the bile into the perfusate, it was injected into the tubing of the system at a distance of about 20 cm. above the aorta of the perfused heart.

RESULTS

In the control experiments the perfused heart continued beating without change in rate, amplitude, or rhythm, for a minimum of four hours.

Sodium taurocholate (Merck), in concentrations of 50 to 200 mg. per liter of perfusate, produced definite changes in the amplitude, rate, and rhythm of the contractions. The amplitude decreased gradually; the rate was slowed; and the arrhythmias observed were of various kinds, such as ventricular alternation, ventricular extrasystoles, blocks of dif-

ferent degrees, and, finally, fibrillation and complete failure of the heart. A concentration of 100 mg. of sodium taurocholate per liter of perfusate consistently brought about almost all of the aforementioned changes in the amplitude, rate, and rhythm within half an hour.

Sodium glycocholate (Mallinckrodt), in concentrations of 50 to 200 mg. per liter of perfusate, also brought about the aforementioned changes

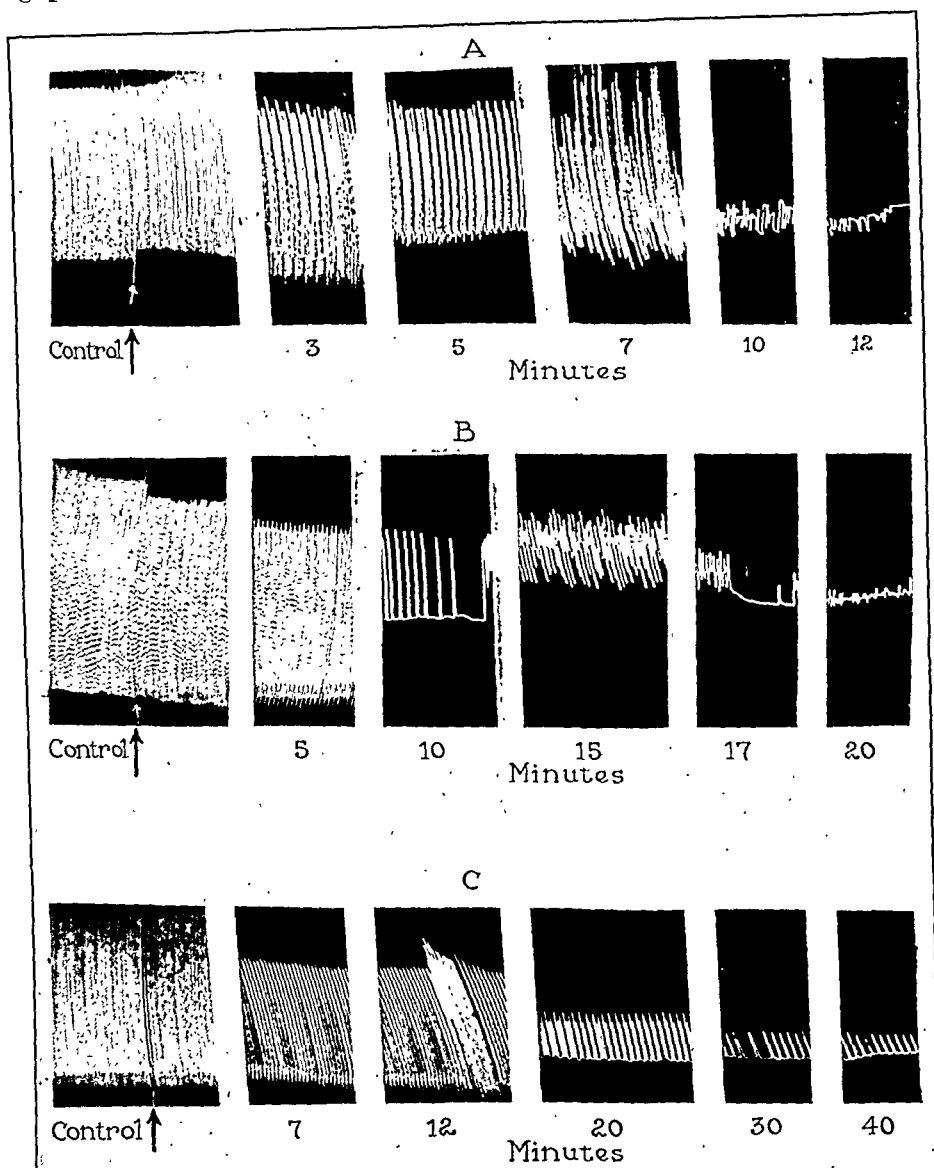


Fig. 1.—Kymographic tracings of the perfused hearts of rabbits under the influence of whole bile and bile salts in the perfusate at a temperature of 38°C . A, Control, arrow indicating the introduction of 3 c.c. of filtered, human, gall bladder bile per liter of perfusate. Successive tracings three, five, seven, ten, and twelve minutes, respectively, after the introduction of the bile. B, Control, arrow indicating the introduction of 100 mg. of sodium taurocholate per liter of perfusate. Successive tracings five, ten, fifteen, seventeen, and twenty minutes, respectively, after the introduction of the sodium taurocholate. C, Control, arrow indicating the introduction of 100 mg. of sodium glycocholate per liter of perfusate. Successive tracings seven, twelve, twenty, thirty, and forty minutes, respectively, after the introduction of the sodium glycocholate.

in rhythm, rate, and amplitude, but took a longer time than the corresponding concentrations of sodium taurocholate.

Whole bile, aspirated from the gall bladder and filtered, when used in concentrations varying from 2.5 to 5 c.c. per liter of perfusate, produced the whole series of the aforementioned changes in less than half an hour, and the heart failed completely much earlier than when bile salts were used. The time required for the appearance of the cardiac disturbances and failure of the heart varied inversely with the concentration of the bile or bile salts in the perfusate.

In several experiments we added 15 c.c. of washed red blood corpuscles per liter of perfusate and observed that the addition slightly delayed the onset of the disturbances of the heart beat produced by the bile salt. Hemolysis of the red blood cells did not occur with the concentration of bile salts used in the perfusate.

When bile was used, it was found that an injection of 0.1 c.c. of filtered gall bladder bile from rabbits, humans, or dogs immediately produced all of the various disturbances in rate, rhythm, and amplitude of the heart beat. Another injection of 0.1 c.c. of bile, given four or five minutes after the first, produced total failure of the heart and complete cessation of its contractions. When 0.5 c.c. of filtered gall bladder bile was injected in one dose, the heart was consistently brought to an absolute standstill in partial systole within a minute. Injections of adrenalin were of no help in any of the attempts at resuscitation of the failing heart.

In order to see whether the increase in the sodium ion concentration, brought about by the addition of the sodium taurocholate or sodium glycocholate, might have any influence on the isolated heart, we ran controls in which corresponding amounts of sodium chloride were added to the original perfusate. The sodium chloride produced no change whatsoever in the rate, amplitude, or rhythm of the contractions.

The results of the experiments were so uniform and definite that it is only necessary to reproduce sample graphs to demonstrate the changes recorded under the influence of whole bile, sodium taurocholate, and sodium glycocholate, when introduced separately into the original perfusate (Fig. 1). In some experiments we observed an initial transient increase in the rate and amplitude of the heart beat immediately after shifting to the perfusate containing whole bile or bile salts. This seems to suggest compliance with the well-known general principle that many substances are stimulating in small amounts over short periods, but toxic or destructive over longer periods and in larger doses.

SUMMARY

A series of experiments were performed on the isolated perfused heart of the rabbit. The changes in cardiac activity were observed, and graphic records were taken to portray the disturbances produced by whole bile and commercial preparations of sodium taurocholate and

sodium glycocholate on the amplitude, rate, and rhythm of the contractions of the perfused heart. Definite and uniform effects were produced. Commercial preparations of bile salts and whole bile from the gall bladders of humans, dogs, and rabbits produced a slowing of the rate of the perfused heart, a diminution in the amplitude of its contractions, and a variety of irregularities in its rhythm, such as ventricular alternation, extrasystoles, and, finally, ventricular fibrillation, ending in complete cardiac failure.

REFERENCES

1. Horrall, O. H.: The Toxicity of Bile, *Physiol. Rev.* 11: 122, 1931.
2. Bunting, C. H., and Brown, W. H.: The Pathology of Intraperitoneal Bile Injections in the Rabbit, *J. Exper. Med.* 14: 445, 1911.
3. Baltaceano, G., and Vasilu, C.: Recherches sur le taurocholate de sodium, *Compt. rend. Soc. de biol.* 115: 1550; Le taurocholate de sodium et les zones réflexogènes sino-carotidiennes, 1552; Le glycocholate de sodium et les zones réflexogènes sino-carotidiennes, 116: 550, 1934.
4. Emerson, W. C.: Toxic Constituent of Bile, *J. Lab. & Clin. Med.* 14: 635, 1929.
5. Horrall, O. H., and Carlson, A. J.: The Toxic Factor in Bile, *Am. J. Physiol.* 85: 591, 1928.
6. Regan, J. F., and Horrall, O. H.: The Physiologic Action of Dehydrocholic Acid, *Am. J. Physiol.* 101: 268, 1933.
7. Still, E. U.: On the Toxicity of Purified Bile Preparations, *Am. J. Physiol.* 88: 729, 1929.
8. Ries, F. A., and Still, E. U.: Toxicity of Purified Bile Preparations. III. Influence on Cardiovascular Responses, *Arch. Int. Med.* 51: 90, 1933.
9. Meltzer, S. J., and Salant, W.: Studies on the Toxicity of Bile. I. The Effects of Intravenous Injections of Bile Upon Blood Pressure, *J. Exper. Med.* 7: 280, 1905. Studies on the Toxicity of Bile. II. The Toxic Effects of Bile Upon the Central Nervous System and the Elimination of Strychnine Through the Bile in Nephrectomized Animals, 8: 127, 1906.
10. Buchbinder, W. C.: Experimental Obstructive Jaundice. III. Age Factor in the Production of Bradycardia, *Arch. Int. Med.* 42: 743, 1928.
11. Baruk, H., and Camus, L.: Action neurotrope expérimentale de biles humaines, recueillies par tubage duodénal, chez le Chat, la Souris, le Pigeon et le Cobaye. Sommeil pathologique; stupeur et troubles végétatifs, *Compt. rend. Soc. de Biol.* 116: 27; Action expérimentale des sels biliaires dans la genèse de certains troubles nerveux produits chez l'animal par injections de biles humaines recueillies par tubage duodénal, 136; Sur un principe toxique cataleptisant décelé dans la bile de tubage duodénal de cinq malades atteints d'ictère. Catatonie et ictère. Données expérimentales et cliniques, 403; Les paralysies biliaires expérimentales, 405, 1934.
12. Bayliss, W. M.: Principles of General Physiology, Ed. 4, London, 1924, p. 211, Longmans, Green, and Company.

CONGENITAL HEART DISEASE

REPORT OF A CASE OF DEXTROPOSITION, PERSISTENCE OF AN EARLY STAGE OF EMBRYONIC DEVELOPMENT OF THE HEART, PERSISTENT TRUNCUS ARTERIOSUS, ABNORMAL SYSTEMIC AND PULMONIC VEINS, AND SUBDIAPHRAGMATIC SITUS INVERSUS

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REPORT OF CASE

Baby boy C. G. was born Aug. 6, 1936, of a primiparous mother, and delivered by emergency cesarean section after a prolonged labor caused by a persistent right occiput posterior position. The birth weight was 8 pounds and 14 ounces. He breathed spontaneously and cried lustily, but his color was not good for twelve hours after birth. His breathing was rapid for several hours following delivery, and cyanotic attacks necessitated the administration of a 5 per cent carbon dioxide and oxygen mixture. He was given 20 c.c. of whole blood intramuscularly three hours after delivery. He was seen by one of us (D. W. G.) about twelve hours after birth. He was a large baby with rather extreme moulding of the head, and he had a large cephalhematoma over the right parieto-occipital region. The lips were slightly cyanotic. The heart sounds were fairly normal but seemed louder on the right side of the thorax than on the left. He was quite drowsy for forty-eight hours and took fluids poorly. He became cyanotic about two or three times in each twenty-four hours, but responded well to the administration of 5 per cent carbon dioxide and oxygen.

He was placed on an evaporated milk formula three days after delivery because of the critical condition of his mother, who subsequently died. His first few days were featured by a great deal of vomiting, sometimes projectile in type, intermittent attacks of cyanosis, diarrhea, and failure to progress in a normal manner. Because of this, and because the heart sounds seemed louder on the right side of the chest, a roentgenogram of the chest was taken six days after birth. This showed that the heart was on the right side. The stomach was found to be on the right side, and a dense shadow interpreted as being the liver was found on the left. Hence a diagnosis of situs inversus viscerum was made. Roentgenologic studies after the ingestion of barium confirmed this diagnosis. He was given several x-ray treatments over the upper chest because of a large superior mediastinal shadow. About ten days after birth, slight cyanosis was present. The hemoglobin was 114 per cent, and the erythrocyte count, 5,860,000. At no time during the baby's thirty-nine-day stay in the hospital was a definite cardiac murmur heard, but, because of the dextrocardia, the persistent cyanosis, the high erythrocyte count and hemoglobin value, and the failure to progress normally, it was felt that severe congenital heart disease was present in addition to the situs inversus. The baby was discharged Sept. 13, 1936, in fair condition, weighing 9 pounds.

At 2 months of age he weighed 10 pounds and 8 ounces. His respiration was quite rapid, and slight cyanosis was constantly present. No heart murmur was heard at this time.

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Received for publication Jan. 27, 1939.

At 3 months his weight was 12 pounds and 3 ounces, and his general condition good. His lips, hands, and feet were cyanotic, though this was not marked. He began to have severe blue spells which came on at irregular intervals. During these spells he jerked his arms but was not unconscious. They lasted approximately four or five minutes. A faint musical murmur was heard over the apex of the heart on the right side for the first time. His erythrocyte count was 5,470,000, and his hemoglobin, 107 per cent.

At 3½ months his weight was 13 pounds and 2 ounces. Definite clubbing of the fingers was noted. Cyanosis of the lips, hands, and feet was more marked. The erythrocytes at this examination numbered 6,020,000, and the hemoglobin was 113 per cent. No murmur was heard.

At 4 months of age his weight was 14 pounds, his erythrocyte count 6,350,000, and his hemoglobin 108 per cent. A twangy systolic murmur was heard in the fourth and fifth intercostal spaces about 2 cm. to the right of the sternum. Severe cyanotic spells were not as frequent but were more prolonged.

His progress for the next three months was good, and at 7 months of age he weighed 16 pounds and 12 ounces. Clubbing of the fingers was more marked, and the nail beds were more deeply cyanotic. Severe cyanotic spells were occurring about once every three or four days and usually lasted about four or five minutes. He seemed to be in severe pain when he had them and would try to jump out of his grandmother's arms in order to get relief.

At 10 months of age he had acute tonsillitis, with fever, from which he recovered in about three days. He sat up alone well at this time. Dyspnea and clubbing were more marked. His hemoglobin was 127 per cent, and the erythrocyte count was 6,501,000 at this time.

When he was 1 year old he weighed 18 pounds. His tissue turgor was poor, and he seemed to wilt in the heat of the second summer. He had not been allowed to walk. Cyanosis and clubbing were marked. His respiration was very rapid, and his face had a pinched expression as if it were hard for him to get enough air. He gained only a few ounces during the next two months. He died while having generalized convulsions, on Oct. 12, 1937, when he was 14 months and 6 days old.

Although it was considered that an electrocardiogram would have been of great interest, it was not possible to take a tracing because of the child's activity and lack of discipline, and anesthesia was deemed inadvisable because of the state of the heart.

AUTOPSY

The general autopsy was done by Dr. N. E. Leake, of the Baptist Memorial Hospital, and the special heart study by one of us (N. S. S.).

The terms right and left, in this description, apply to the right and left sides of the body.

The Heart.—The heart was found to be in the dextroposition (Fig. 1), lying within a pericardial sac which was apparently normal. There were no signs of pericarditis on the surface of the organ. Two auricles were present, the right and left. The left auricle had a small appendage which presented anteriorly and contained no clots. At its upper end there was a fairly large venous inlet, 5 mm. in diameter (Fig. 2). At its lower portion there was another venous inlet, approximately 6 mm. in diameter, which came up through the diaphragm from the liver. One of the larger tributaries was apparently the inferior vena cava and could be traced by probe posterior to the liver. The interauricular septum (Figs. 3 and 4) was incomplete; its free edge was crescentic, with convexity upward, and it ran from the posterior wall to the anterior wall of the heart. It was 2.5 mm. thick at its edge. Five millimeters above this free border was the lower edge of a patent foramen ovale, which was 7 mm. in its long diameter. The right auricle had a small

appendage, without clot, which presented anteriorly. It was somewhat smaller than the left, and its inner surface was trabeculated except on the septal and anterior surfaces, where it was smooth. At its upper end there was a venous entrance about 4 or 5 mm. in diameter, so situated that the main blood stream could go fairly directly through the patent foramen ovale into the left auricle.

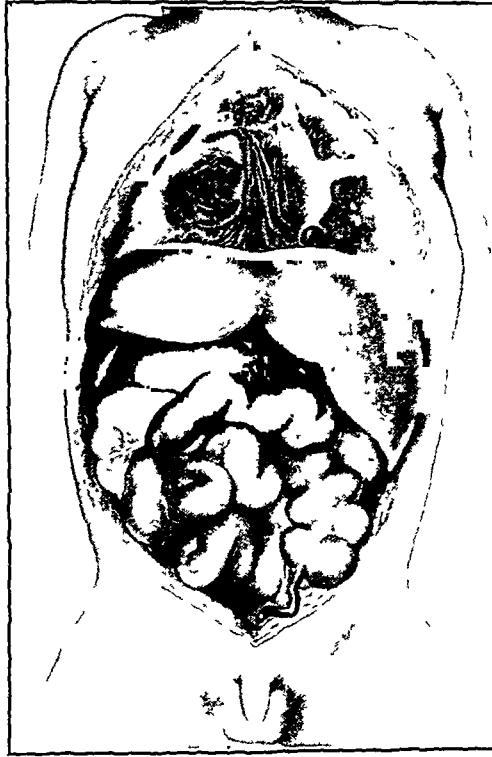


Fig. 1.—This illustration shows the situs inversus below the diaphragm and the dextroposition of the heart. The azygos lobe of the left lung is clearly portrayed.

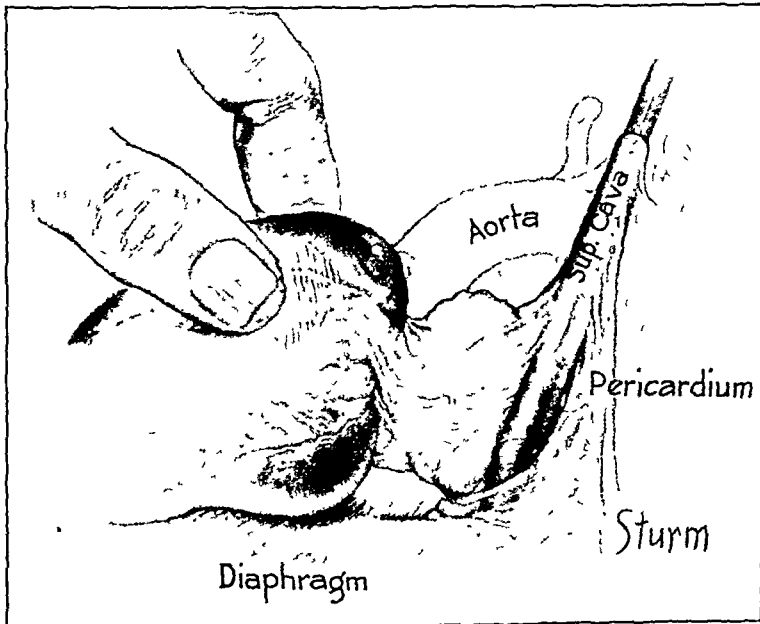


Fig. 2.—The heart is pulled to the right, showing the superior cava on the left (exaggerated by a probe).



Fig. 3.—The opened heart. See Fig. 4 for the names of the parts and the course of the blood flow.

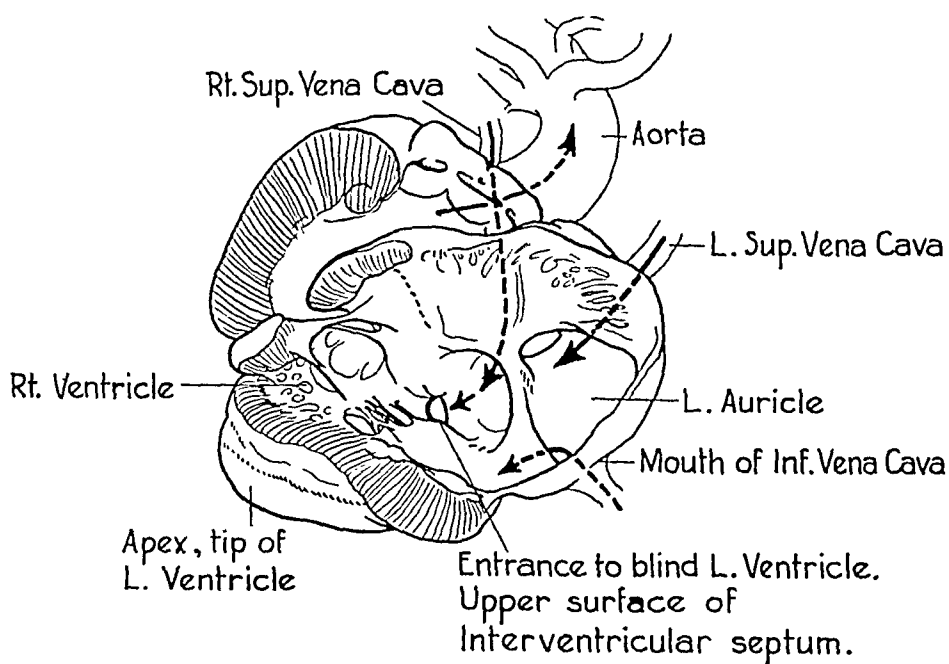


Fig. 4.—Sketch of the opened heart (see Fig. 3), showing the chambers and parts, and indicating by arrows the course of the blood flow.

Immediately below the defective interauricular septum there was a defective interventricular septum with crescentic border curving downward instead of upward. To the left of this border there was an opening into a small left ventricle. This entrance was guarded by one normal, thin valve on its left wall, and portions of two other valves which rode over the septal margin and continued into the right ventricle. Apparently, when the heart contracted these valves floated up and prevented regurgitation into the auricles, but at that time they were sufficiently elevated above the septal margin to allow blood to flow from the left ventricle into the right ventricle. This was the only outlet from the left ventricle. The left ventricle formed the apex of the heart.

The two valves which rode over the septum, together with another valve which came down the middle of the right ventricle to be attached to a papillary muscle arising almost from the apex, were the valves of the right ventricle. The portion of the ventricle between these valves and their chordae was apparently smaller than that part of this same ventricle which lay anteriorly and to the right. This larger portion of the right ventricle emptied into a single aorta, which was guarded by three apparently normal aortic cusps. Two coronary orifices, arising from the posterior and right sinuses of Valsalva, respectively, were apparently normal. The coronary arteries were not traced farther.

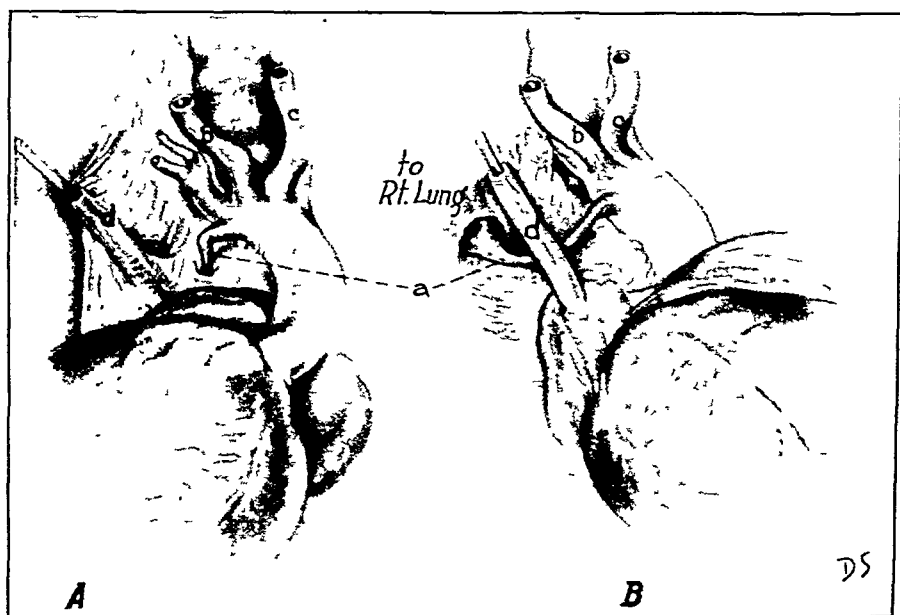


Fig. 5.—The truncus and its first branches: *a*, right pulmonary artery; *b* and *c*, branches to upper portion of the body; *d*, right superior vena cava. *A* and *B* represent different stages of dissection and different aspects of the specimen.

The Aorta and Pulmonary Arteries.—The aorta, or truncus itself, was lined with normal, smooth endothelium. It was approximately 10 mm. in diameter at its origin. It pointed upward and to the left and arched back in the same general direction and manner as the normal human adult aorta. There was only this one outlet from the heart, however, and it remained intact for three centimeters. At this point (Figs. 5 and 6) its branches began. A common trunk on the right gave rise to three vessels which diverged almost immediately. The first (Fig. 5*a*) went straight to the right and ran to the hilum of the lung. It lay posterior to the vein which emptied into the right auricle. It was rather small, tapering off to an external diameter of 2 mm. at its midportion, but becoming larger at the hilum, where the flattened artery was 5 mm. across. The middle vessel proceeded upward,

and, after a distance of 10 mm., it divided into two branches. The third vessel, as far as could be seen in the specimen, remained single. These vessels were both 3 mm. in external diameter. What parts were supplied by these arteries (Fig. 5, *b* and *c*) was not ascertained before the organ was removed.

Just to the left of the common trunk from which these three vessels originated, and in the angle it formed with the aorta, another vessel, 3 mm. in diameter, arose. Above this point, naturally, the aorta became smaller. Five millimeters higher on the superior surface of the arch two vessels arose almost by a common trunk (Fig. 6, *b* and *c*), one 2 mm., and one 3 mm., in diameter. Opposite these two vessels on the posterior undersurface of the arch, there arose another artery 3 mm. in diameter, which curved posteriorly and downward for a distance of approximately 1 cm., and then turned sharply to the left to the hilum of the left lung (Fig. 6, *c*). This artery promptly divided into much larger branches than its parent stem, the lower flattened artery being 9 mm. across, the upper 5 mm. In the elbow formed by this artery there were two veins, to be described later, which emptied into the left "superior cava." From this point on, the aorta continued its arch without further important branches.

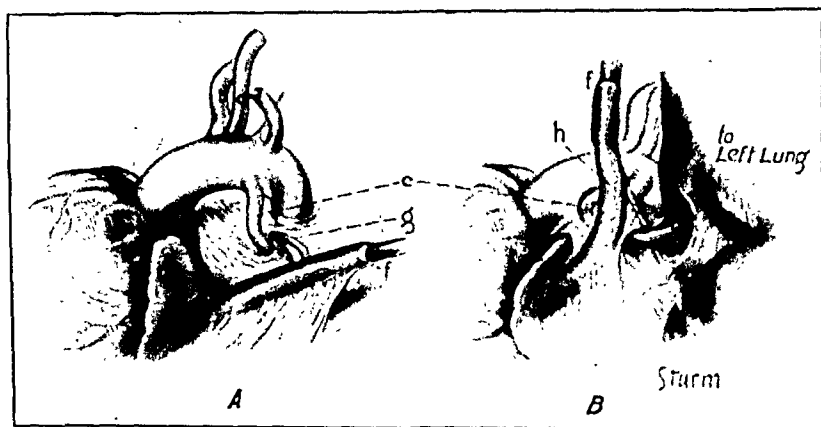


Fig. 6.—The truncus and its later branches. *b* and *c*, other arteries to the upper parts of the body; *c*, the left pulmonary artery; *f*, the left superior vena cava; *g*, the pulmonary vein entering the left superior vena cava; *h*, vein from the posterior mediastinum. *A* and *B* represent different stages of the dissection and different aspects of the specimen.

The Systemic Veins.—The inferior cava was on the left side, and entered the left auricle from below. Into it drained, as usual, the veins from the liver. The left superior cava emptied into the upper portion of the left auricle. Two centimeters above the auricle, there opened into this superior cava from the right a vessel which carried all of the oxygenated blood returning from the lungs (Fig. 6, *g*). One and one-half centimeters above this there was a smaller vessel entering from the right which could be traced downward in the posterior mediastinum and was lost on the posterior wall of the esophagus (Fig. 6, *h*). In the intact specimen the superior cava lay adjacent to, and somewhat posterior and to the left of, the first portion of the truncus. The superior cava passed down anterior to the pulmonary vessels and the left main bronchus.

On the right there was another superior cava which emptied into the upper aspect of the right auricle. It was about one-half the size of the left cava. It lay about 1 cm. away from the first portion of the truncus and posterior and to the right of it. It passed in front of the right pulmonary artery and the hilum of the lung. A small tributary from the mediastinum entered on its posterior surface. This cava evidently drained the right side of the neck and head.

The Pulmonary Veins.—Two pulmonary veins emerged from each lung and on each side joined to form a single vessel (Fig. 7). These vessels approached each other in the mediastinum posterior to the heart and pericardium. The right and left vessel met, and from the upper border there emerged a single vein which passed upward and to the left behind the left main bronchus and under the arch of the truncus. It then curved forward and down to the left across the left pulmonary artery and entered the left superior cava as described before (Fig. 6, *g*). This vessel became quite narrow, its flattened width being only 2 mm. as it passed over the bronchus. It was wider posteriorly and anteriorly.

The Lungs.—The left lung was composed of three lobes. The upper was fairly large and occupied the superior and posterior half of the chest. The lower was of about the same size and occupied the inferior half of the chest. The fissure between these two lobes ran anteriorly about one-half the way and then passed anteriorly and upward toward the apex, separating from the upper lobe a small third lobe which lay anteriorly. The caudal end of this small and narrow lobe lay for a short distance against the lower lobe. This was the azygos lobe.

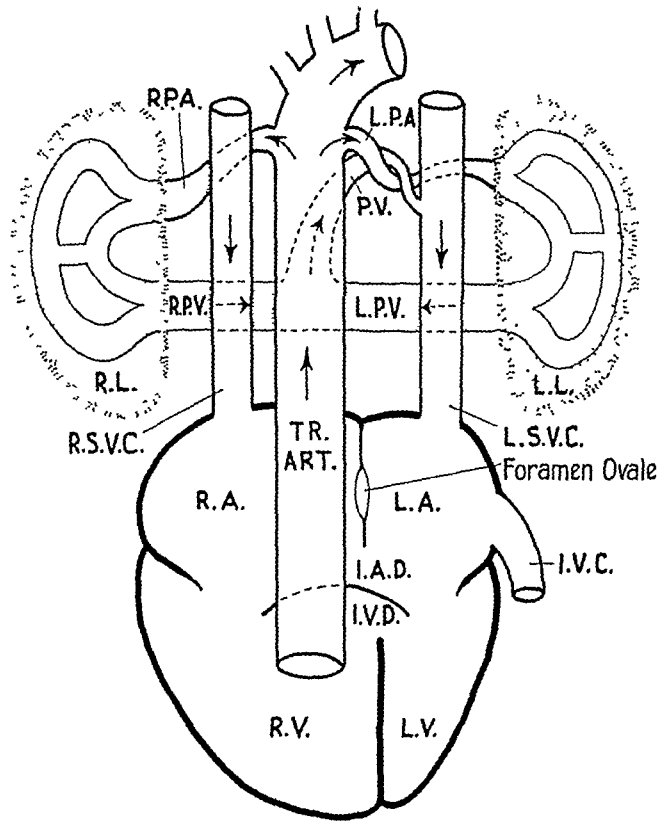


Fig. 7.—Diagram of the heart and vessels, showing the circulation: *I.A.D.*, interauricular septal defect; *I.V.C.*, inferior vena cava; *I.V.D.*, interventricular septal defect; *L.A.*, left auricle; *L.L.*, left lung; *L.P.A.*, left pulmonary artery; *L.P.V.*, left pulmonary vein; *L.S.V.C.*, left superior vena cava; *L.V.*, left ventricle; *P.V.*, pulmonary vein; *R.A.*, right auricle; *R.L.*, right lung; *R.P.A.*, right pulmonary artery; *R.P.V.*, right pulmonary veins; *R.S.V.C.*, right superior vena cava; *R.V.*, right ventricle; *Tr. art.*, truncus arteriosus.

The right lung was composed of three lobes whose fissures ran as in the normal pattern. The middle lobe was smaller than usual because the heart occupied a portion of this side of the chest. There were adhesions of the undersurface of this lung to the upper surface of the diaphragm.

The kidneys were essentially negative except that the left kidney had rather dark markings in the inferior half, and near the lower pole there was a small, dark, pos-

sibly hemorrhagic area. The right kidney was approximately the same. Both kidneys showed definite fetal lobulation. The capsules stripped easily.

The organs were not weighed; the thoracic and abdominal organs have been retained intact.

DISCUSSION

The Heart.—Two types of dextrocardia are recognized. In the type which Abbott¹ classifies as *a*, “the heart is not transposed, but presents simply a persistence of the embryonic stage in which the heart lies more to the right, and its apex is formed by the right half of the common ventricle.” The heart “appears to have undergone a simple rotation from left to right on its vertical axis, so that its left chambers come to lie more anteriorly and its right chambers more posteriorly.” “This, which is not a true transposition, is the condition present in the majority of the cases of congenital dextrocardia *without situs inversus*. In these cases the heart is usually the seat of grave associated anomalies.”

In Abbott's second, or *b*, type, there is a complete reversal of all parts, so that the heart presents a mirror image of the usual condition. “In complete *situs inversus* this ‘mirror’ condition is the rule, but true transposition of the heart only, without *situs inversus*, is exceedingly rare.”

The presence of *situs inversus* in our case suggests that the dextrocardia might be of the mirror-image type. Two facts, however, are against this interpretation. The apex was not formed by the right ventricle, but by the left, although the latter was the smaller of the two. In the second place, the persistent truncus arteriosus curved to the left and followed the course of the normal aorta. If the inversion were complete in all respects, it would be expected that the aortic arch would curve to the right and pass down along the right side of the vertebral column. It might be expected that there would be reversal of the lungs also, with three lobes on the left instead of the right, and an azygos lobe, if present, on the right. In the present case the reversal did not exist; the normal three lobes remained on the right, and the usual two lobes, with the azygos lobe, were on the left.

On the other hand, neither does the case here described fulfill all of the requirements for inclusion in Type *a*. In the first place, *situs inversus* was present, which is usually not the case in this type. Secondly, there was no “simple rotation” from left to right, bringing the left ventricle anterior. The left ventricle remained posterior and on the left side of the heart.

According to Frazer,² the human embryonic heart in the sixth week is characterized by these features: the heart as a whole lies largely to the right; the right ventricle is larger than the left and is the origin of the truncus; the truncus passes upward and to the left; the small left ventricle empties only over the incompleting interventricular septum. All of these characteristics existed in this heart, so that the conclusion is obvious that it represents the persistence of a normal stage of develop-

ment of the embryo. That the apex was formed by the left ventricle rather than the larger right may probably be ascribed to the growth of the left ventricle during the later stages of prenatal, and the fourteen months of extrauterine, existence.

This heart does meet, then, the important criteria of Type *a* dextrocardia; it lay largely to the right and presented a persistence of a normal stage of embryonic development with "grave associated anomalies."

If this classification is correct, and the lungs are not reversed, there exists the very unusual condition of situs inversus below the diaphragm, but no inversion of the organs above.

That the heart lay largely to the right rather than to the left may have been due, in part, at least, to the levoposition of the liver. The left lobe was thus higher than the right, which would crowd the heart from the left into the roomier right chest.

The inferior cava emptied into the heart on the left instead of the right. The inverted position of the abdominal organs explains this. In an early stage there are two postcardinal veins. With the bulk of the liver developing on the left, it is easy to understand why the right postcardinal vein should atrophy and disappear, leaving the left alone to carry the return flow of all subdiaphragmatic blood.

Further evidences of the persistence of the fifth-sixth week embryonic stage were the incompleteness of both the interauricular and the interventricular septa, the development of the foramen ovale in preparation for the completion of the interauricular septum, and the small size of the left ventricle, which has no function until the truncus has been divided into the two aortae.

The Truncus.—According to Abbott,³ "Gierke suggests that the presence of four semilunar cusps . . . is positive proof of an undivided primitive arterial trunk, while the presence of three semilunar cusps . . . argues that development of the aortic septum has occurred and that obliteration of one or other of the vessels had taken place as a secondary event." In the case here reported, the origin of the truncus was guarded by three normal semilunar valves. No structure was found that might have been the remnant of the pulmonary artery. No ridges or signs of division were present in the truncus. The presence of the three valves, instead of four, was the only suggestion that this was not an absolutely true persistence of the primitive truncus. Otherwise, it definitely falls into the classification of this rare anomaly in which Abbott⁴ includes twenty-one of her 1,000 rare cases of congenital heart disease.

The truncus itself was a single vessel without any evidence of division or attempts at division. Three centimeters above its origin there arose two vessels, one on the right and one on the left, which were the only sources of blood supply to the lungs. These represented the remnants of the sixth aortic arches, from which the pulmonary arteries develop.

This state of development is that present in the human embryo at the age of about five to six weeks, and is comparable to the adult condition in the frog. The branches above these pulmonary arteries supply the upper portions of the body. Since they were severed in doing the autopsy, their distribution can only be assumed.

It is of interest to note that these pulmonary vessels entered the hilum of the lungs anterior to the main bronchi.

The Systemic Veins.—In the early stages of development of the embryo, the sinus venosus is found to be a sort of pool, into which empty a right and a left precardinal vein and a right and a left postcardinal vein. In embryos of six to eight weeks of age the atria have developed much more rapidly in size than the sinus venosus, and incorporate the latter into the auricular wall. At the same time, the left precardinal and postcardinal veins usually atrophy and disappear, so that, at about seven weeks, the blood from the head end of the embryo returns to the heart by the right precardinal vein, now become the superior vena cava, and the blood from the caudal end returns by the right postcardinal vein, now become the inferior vena cava.⁵

In our case, development evidently ceased at the fifth or sixth week. Both precardinal veins persisted, but the left was larger than the right. The sinus venosus was taken up by the auricular wall. The left postcardinal vein persisted as the inferior vena cava because of the situs inversus, and the right, having no function, atrophied and disappeared. If the heart had continued its development and the septa had been completed, only the smaller right superior cava would have emptied into the right atrium; and the larger superior cava on the left and the inferior vena cava would both have emptied into the left atrium.

The blood that entered the heart by these channels, however, was not all systemic blood. The return flow from the lungs was poured into the left superior cava and then was mixed further with the systemic blood in the communicating chambers of the heart. The case can therefore be said to belong to the group of congenital heart disease with cyanosis.

The mixed blood passed from the heart into the truncus, and from thence part of it went through the branches to the lungs, as described above, and the rest to the various parts of the body.

The Pulmonary Veins.—There is evidently some difference of opinion as to the origin of the pulmonary veins. According to Flint,⁶ who made careful studies of the pig embryo, the pulmonary veins start in the 5 mm. pig as a single outgrowth from the posterior wall of the undivided auricle. In the 6 mm. pig, the auricular septum has grown enough to indicate that this vessel empties into the left auricle. In the 7.5 mm. embryo, two small tributaries are seen, which are lost in the capillary plexus about the headgut, thus establishing a drainage system from the pulmonary anlage.

Schmidt,⁷ according to His, reported a single vessel entering the left auricle of a human embryo. The earliest embryo examined by His⁸ himself already had four pulmonary veins. The rapid enlargement of the auricle engulfs the single and double branches, so that eventually there are normally in the adult four pulmonary veins entering the auricle directly.

Keith,⁹ in his recent textbook, makes the statement that "the pulmonary veins grow out from the pulmonary buds, and enter the left auricle through the venous mesocardium about the fifth week."

In the case here presented the manner of drainage of the pulmonary veins was so unusual that it is difficult to explain. If the primordial vein grew from the auricle, then branched to reach the pulmonary capillaries, it must follow that this main stock eventually atrophied and disappeared, leaving the right and left branches joined in the midline. These sought an outlet through the devious capillaries about the pulmonary anlage and eventually followed the bizarre pathway here found. If the theory of Keith is correct, the vessel entering the auricle never existed in this case, but the vessels developed from the pulmonary bud areas, joined in the midline, and then followed the bizarre pathway to the left superior vena cava, instead of reaching the auricle.

According to Thoma, as translated by Flint,¹⁰ it has been "found in the chick that arteries and veins are originally simple capillaries. The subsequent transformation of the latter into arteries, on the one hand, and veins, on the other, is due to their fortuitous location with reference to the primitive aortae and the venous ostia of the heart. Their growth in size bears a definite relationship to the velocity of the current in them, while their arterial or venous nature is determined by the character of the current . . . (which) depends naturally on its position on the arterial or venous side of the capillary plexus."

When development ceases and growth continues, unusual tensions may be put on the pathways the blood usually takes. This may prove an obstacle to easy blood flow, and the blood seeks an outlet with less resistance through other and unusual channels in the capillary plexus. With the enlargement of the new channels because of the velocity and volume of the stream through them, their growth is stimulated further, while the normal pathways, carrying less and less blood, eventually atrophy and disappear.

SUMMARY

A case of congenital malformations with several unusual features is reported. These features include situs inversus viscerum below the diaphragm but not above; dextroposition of the heart; cessation of development of the heart at the fifth-sixth week stage of embryonic development; persistence of a truncus arteriosus with pulmonary arteries branching from this; two superior venae cavae and a left-sided inferior vena cava; and very abnormal pulmonary veins.

REFERENCES

1. Abbott: Osler's Modern Medicine, Lea and Febiger, Philadelphia, 1937, Vol. 4: p. 661.
2. Frazer, J. E.: The Formation of the Pars Membranacea Septi, J. Anat. and Physiol. 51: 19, 1916.
3. Abbott: Osler's Modern Medicine, Lea and Febiger, Philadelphia, 1937, Vol. 4: p. 710.
4. White, Paul D.: Heart Disease, New York, 1937, 2nd ed. The Macmillan Co., Abbott's table opposite p. 185.
5. Arey, L. B.: Developmental Anatomy, Philadelphia, 1930, 2nd ed., W. B. Saunders Co., p. 269.
6. Flint, J. M.: The Development of the Lungs, Am. J. Anat. 6: 62, 1906.
7. Schmidt, F., and His, W.: Reports a German reference to the original Danish work in Jahresbericht von Virchow-Hirsch f.d.j. 1871, l. s. 65.
8. His, W.: Zur Bildungsgeschichte der Lungen beim menschlichen Embryo, Arch. f. Anat. und Phys., Anat. Abt. 89, 1887.
9. Keith, Sir A.: Human Embryology and Morphology, Baltimore, 1933, 5th ed., Wm. Wood & Co., p. 396.
10. Flint, J. M.: The Development of the Lungs, Am. J. Anat. 6: 60, 1906.

MEDIONECROSIS AORTAE IDIOPATHICA CYSTICA

REPORT OF A CASE, WITH "HEALED" DISSECTING ANEURYSM

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CYSTIC necrosis of the aortic media is a rarely recognized disease which was first described in 1929 by Erdheim.^{1, 2} The cystic degeneration develops in focal accumulations of chromatophic or mucoid material, with tearing of the elastic laminae of the media and with some evidence of reparatory proliferation of connective tissues. The only thorough review of the pathology of the condition which has been published in English is that of Moritz.³ He found only twelve cases,⁴⁻⁹ up to 1932, including three of his own. Glendy, Castleman, and White¹⁰ described typical cystic medionecrosis in eight of their nineteen cases of ruptured dissecting aneurysm; in the others, adequate histologic study had not been made. The condition was present in all five of the cases of "spontaneous" rupture of the aorta due to dissecting aneurysm reported by Klotz and Simpson.¹¹ Gobel²⁵ and Milew²⁶ have reported single cases.

Thus, twenty-seven cases of cystic medionecrosis have been found in the literature. All of the patients died from rupture of a dissecting aneurysm. It is evident, therefore, that the condition is of great pathogenic or etiologic significance in dissecting aneurysms. This pathogenic relationship has been overlooked in the otherwise thorough recent reviews of dissecting aneurysm.^{12, 13, 14}

The purpose of this paper is to report a case of "healed" dissecting aneurysm due to idiopathic cystic medionecrosis of the aorta, in which the clinical and pathologic features were sufficiently distinctive to suggest the possibility of making the diagnosis during life.

REPORT OF CASE

Walter D., No. 100-525, a 33-year-old white man, entered Lakeside Hospital Jan. 23, 1937, suffering from severe cardiac decompensation. This was thought to be due to syphilitic aortic insufficiency with a bizarre valvular lesion. On the third hospital day, while lying quietly in bed, he suddenly complained of being dizzy, sat upright, and died almost immediately.

Past History.—In August, 1928, he contracted syphilis. Intensive antisyphilitic treatment was given here from September, 1928, until November, 1931, during which time he received thirty-three injections of bismuth, forty-seven injections of arsenicals, and eleven injections of mercuric salicylate, besides mercury rubs and iodides. After April, 1930, his blood and spinal fluid Wassermann reactions were repeatedly negative. On frequent examinations no abnormality of the heart was

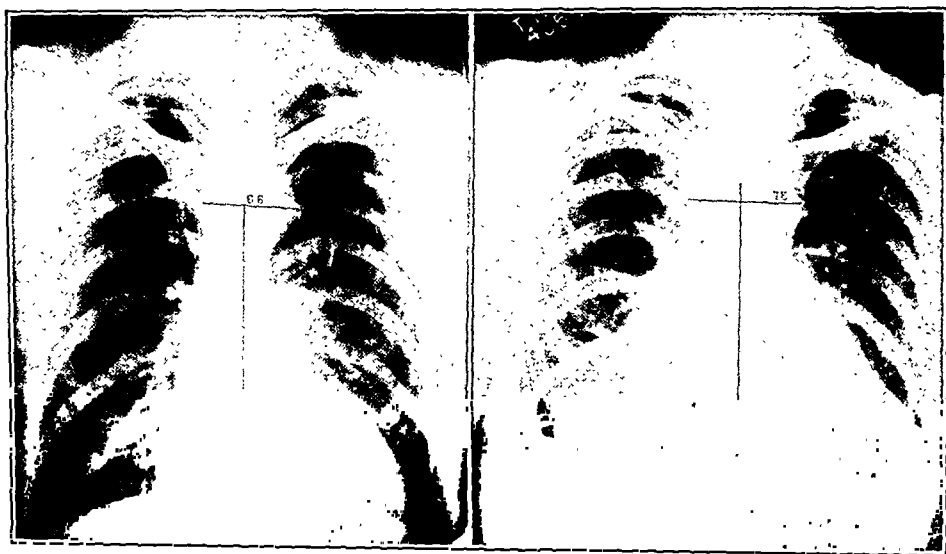
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Received for publication Feb. 6, 1939.

ever detected; his blood pressure was always within the normal range. In October, 1933, a soft systolic murmur was heard over the aortic area.

Present Illness.—On Feb. 19, 1934, while carrying a heavy basket on his job as a train porter, he suddenly suffered from severe substernal pain of an oppressive nature, extreme weakness, dizziness, shortness of breath, palpitation, chilliness, and muscular pains. The physical signs were those of highly developed aortic regurgitation, with a very marked diastolic aortic thrill and an Austin Flint murmur. In addition, there was also a very intense systolic thrill of a peculiar vibratory nature, and a long, coarse, whistling systolic murmur over the aortic area and neck vessels. The blood pressure was 160/30. Syphilis was thought to be the sole cause. The extremely loud murmurs and intense thrills suggested the possibility of rupture of an aortic valve cusp. During the next two years he was a cardiac invalid, but remained in fairly good condition except for frequent, transient exacerbations of symptoms. These responded well to rest in bed, digitalis, sedatives, iodide, and bismuth. The physical findings remained about the same except for the appearance of a difference in blood pressure in the two arms, e.g., 160/40 in the right arm and 200/40 in the left. Progressive enlargement (Fig. 1.) of the whole heart and the great vessels was demonstrated by percussion and fluoroscopy.



A.

B.

Fig. 1.—Roentgenograms of the chest, showing the progressive enlargement of the heart and aorta between the time of the onset of symptoms and death. A. March, 1934; B. November, 1936.

Heart sound tracings (Fig. 2) showed, at the apex, a double component to the second sound, with a marked diastolic murmur which was greatly accentuated in presystole, while at the aortic area there were a coarse diastolic murmur in presystole and a systolic murmur. Subclavian pulse tracings, which also suggested that the valvular lesion was peculiar in structure, showed a free ejection phase as in syphilitic aortic insufficiency, but there was also a sharp incisura near the bottom of the catacrotic limb. This indicated that the aortic valve was functioning and is taken as evidence of ring dilatation rather than valve distortion of either the rheumatic or syphilitic type. The electrocardiogram was normal, except for increasing left axis deviation and the presence of U waves.

In November, 1936, serious decompensation developed for the first time, with edema of the ankles and legs and an enormous increase in the size of the heart. The

heart sounds and murmurs were much louder and the thrills and shocks more intense than before. The change in character of the sounds and murmurs strongly suggested the possibility of rupture of an aortic cusp. In December, 1936, congestive heart failure began to progress rapidly. There was constant pain in the right lower chest, under the sternum, and over the precordium. On December 31, 1936, severe shooting pains began in the lower part of his back. These lumbar pains increased daily, and he complained of "something wrong in his stomach." His arms felt "weak and dead-like" and his feet were very cold. On Jan. 23, 1937, the pain in the epigastrium and lumbar region became so severe that morphine in large doses was required for relief. Three days later he died with dramatic suddenness.

AUTOPSY

Post-mortem diagnoses: Idiopathic cystic medionecrosis of the aorta, with numerous, small, dissecting aneurysms of the descending abdominal aorta; rupture of the ascending aorta; healed focal dissection of the ascending aorta, with formation of a transverse projection into the lumen; hemopericardium (800 c.c.); left-sided hemothorax (400 c.c.); hypertrophy and dilatation of the heart (weight, 960 gm.); insufficiency of the aortic valve due to dilatation of the valvular ring; hyperemia of the lungs and liver; remote infarcts of the lower lobe of the right lung.

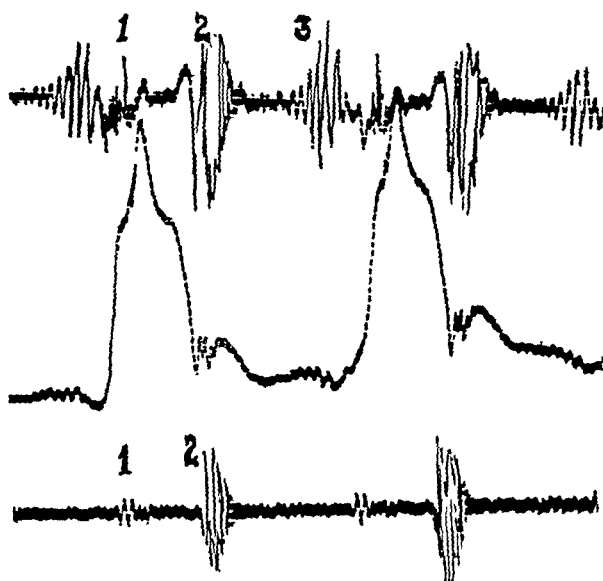


Fig. 2.—*Lower curve:* Heart sound tracings made with the receiver over the aortic area, showing systolic (1) and diastolic (2) murmurs. *Middle curve:* Subclavian pulse curve, showing the sharp ejection phase and the marked incisura near the bottom of the catacrotic limb. *Upper curve:* Heart sound tracings made with the receiver over the apex, showing the systolic murmur (1) and the two components (2 and 3) of the diastolic murmur.

Heart.—Greatly enlarged in all chambers, measuring 20 cm. from base to apex and 14 cm. across the base. Both ventricles were greatly hypertrophied and dilated; the wall of the right ventricle was 16 mm. thick, that of the left 32 mm. The myocardium appeared firm and of normal color, with no gross infarction. The columnae carneae and pectinate muscles were flattened. The papillary muscles were essentially normal. The chordae tendineae were not thickened, shortened, or adherent. The cusps of the mitral, tricuspid, and pulmonary valves were thin, delicate, and showed no abnormalities. The aortic valvular ring was moderately dilated, measuring 9 cm. in circumference. The aortic semilunar cusps were large, not deformed, and were not separated from each other or fused at the commissures. There was no evidence of syphilitic or rheumatic valvulitis. Aside from being greatly distended, the coronary arteries and veins were normal.

The aorta showed none of the typical changes of syphilis or advanced arteriosclerosis. The entire ascending aorta formed a fusiform aneurysm which measured about 12 cm. in circumference. On the intimal surface there were large transverse tears in eight places in the ascending aorta, in one place in the arch just distal to the origin of the left subclavian artery, and in five places in the lumbar portion of the abdominal aorta. These transverse tears extended through the intima and for a short distance into the media. Several were deeper, extending at least halfway through the media; in these the media was split and slightly elevated above and below the tear (Figs. 3, 5, 6). Evidently these were beginning dissections. Through one of the

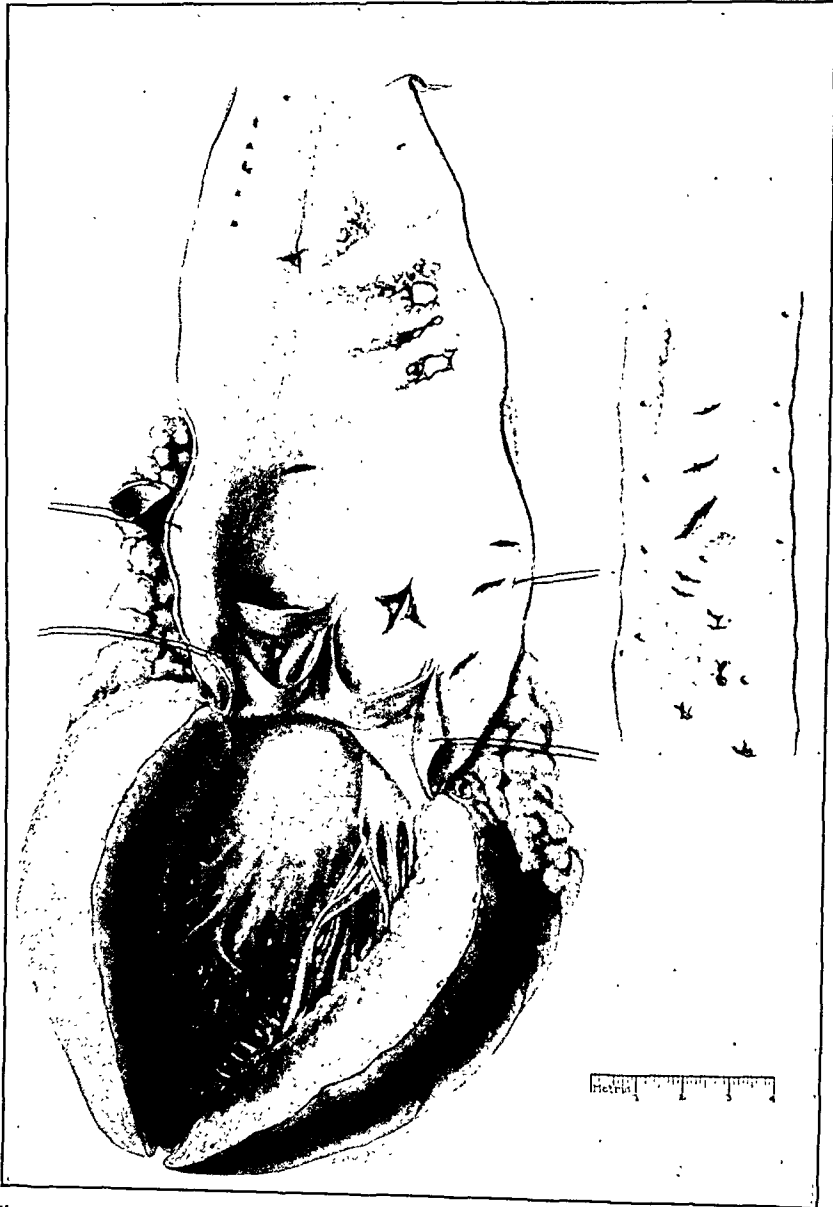


Fig. 3.—Drawing of the heart and aorta, showing the transverse, shelflike projection just above the right coronary orifice, produced by a healed, focal, medial dissection. Also shown are the numerous transverse intimal fissures in the ascending aorta and in the lumbar abdominal aorta (inset). Through one of these fissures, above the noncoronary cusp, the rupture of the ascending aorta occurred.

lowermost of the transverse tears in the ascending aorta, 3.5 cm. above the left coronary cusp, there was a rupture through the entire wall of the vessel (Fig. 3.). This was in the long axis of the transverse tear and was the only rupture of the aorta. Through it, approximately 800 c.c. of blood had escaped into the pericardial cavity, resulting in cardiac tamponade.

Immediately above the origin of the right coronary artery there was a large transverse projection (Figs. 3 and 4) which was fairly smooth on both surfaces. This shelflike fold was fairly stiff and inelastic, and projected 1 cm. into the lumen of the aorta. It was semilunar, and so similar to an aortic valvular cusp that at first it was mistaken for a supernumerary right coronary cusp. Just above this transverse fold the intima was eroded or dissected away, leaving a rough, wrinkled area 6 by 7 cm. in size.

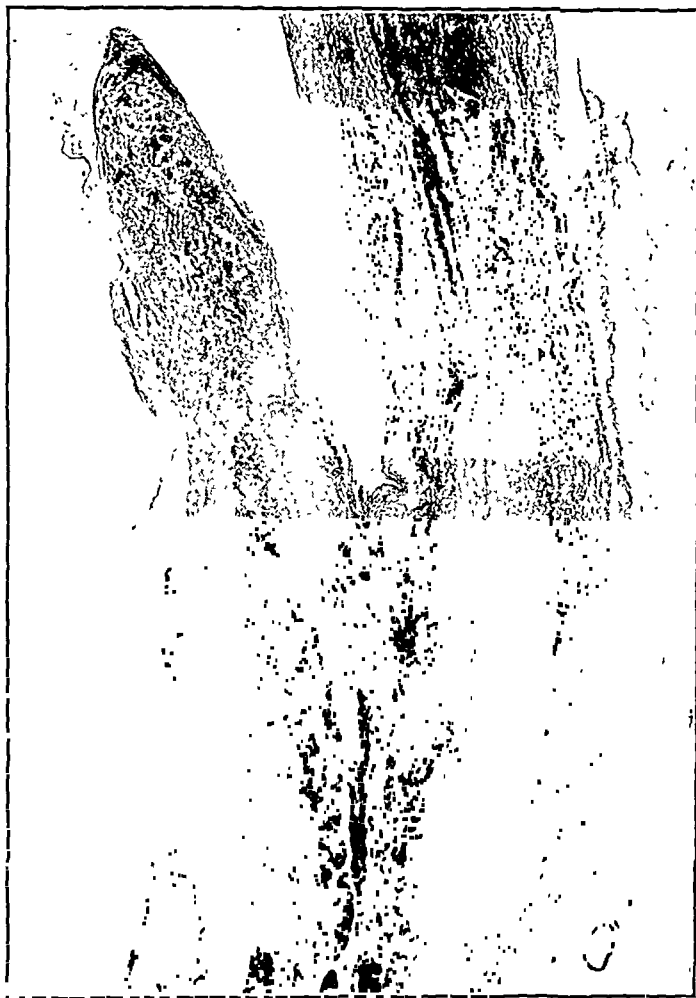


Fig. 4.—Photomicrograph of longitudinal section through the wall of the ascending aorta at site of the transverse shelf. Note the marked cystic degeneration in the media, with rupture of elastic laminae. The edge of the right coronary cusp of the aortic valve is seen at the left, near the bottom. Weigert elastic stain; magnification, 18 diameters.

The remainder of the thoracic aorta, and especially the lower lumbar portion of the abdominal aorta, showed a few irregular atheromatous plaques of small size and a few small areas of wrinkling, but in general it was quite smooth and entirely devoid of evidence of syphilitic aortitis. No thrombi were present.

Microscopic Examination.—Sections from many portions of the aorta showed focal accumulations of chromatrophic material between the elastic laminae of the media throughout the entire vessel. In most places this material contained minute vesicles, and frequently there were larger cavities apparently formed by fusion of adjacent vesicles. Generally, the intima appeared normal, and nowhere did the adventitia show significant changes. The vasa vasorum showed no endothelial proliferation, and there were no perivascular cellular infiltrations.

Sections through the regions of the transverse tears of the intima and media in both the ascending and abdominal aorta showed the characteristic changes of "medionecrosis aortae idiopathica cystica," as described by Erdheim,^{1,2} Moritz,³ and others. The fissures were due to tearing of the intima and about half the thickness of the media. In these places the chromatrophic accumulations between the elastic laminae of the media were more abundant, and showed necrosis with formation of cysts of various sizes. Many of the cysts were large enough to be visible with the unaided eye, and often measured as much as 5 or 6 mm. in length by 1 or 2 mm. in width. The elastic laminae were ruptured near the edges of the cysts, leaving loose ends and spurs of elastic tissue projecting into the cavities. Short pieces of elastic tissue were seen free in some cysts. The unruptured elastic tissue bundles appeared broken up into tiny globular masses with loss of fibrillar structure.

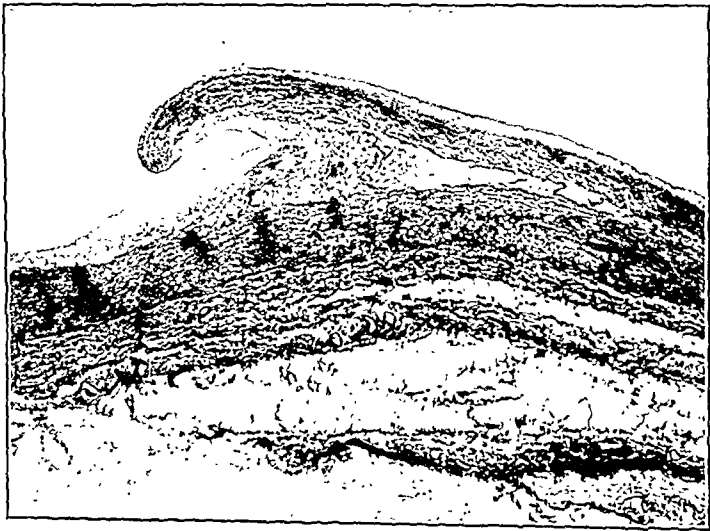


Fig. 5.—Photomicrograph of longitudinal section of the aorta at site of a transverse fissure, showing the "lipping" of the elevated media and intima by a beginning dissection through the diseased tissue in the middle portion of the media. Various degrees of cystic degeneration and repair are seen. Van Gieson connective tissue stain. See text for more detailed description. Magnification, 18 diameters.

The larger cysts, especially those underlying the intimal tears, usually showed more or less production of collagenous tissue, with irregularly arranged young fibroblasts. The arrangement of these cells and fibers was sometimes at right angles to the axis of splitting of the media by the cystic necrosis, and their appearance suggested healing by strengthening of the disrupted elastic laminae. There was no evidence of proliferation of elastic tissue. In these areas of collagenous proliferation there was often secondary necrosis. The cystic degeneration was most marked in the neighborhood of the middle third of the muscular coat. This was the level at which splitting always occurred, never between media and intima or between media and adventitia.

The transverse fold of tissue (Figs. 3 and 4) just above the aortic valve was seen microscopically to have been produced by dissection of the inner half of the media along a line of most advanced cystic medionecrosis. The fold itself consisted of the endothelium and subendothelium of the intima on its proximal, or cardiac, side, plus about one third of the thickness of the media. The rough area just above the fold showed only the thin remaining portion of the media, together with an irregular endothelial covering. The presence of endothelium here and on the distal surface of the fold showed that the dissection of the media resulting in this anomaly had occurred long enough before death to permit repair of the surface.

The cystic degeneration in the proximal portion of the ascending aorta was more extensive than anywhere else. Here many of the larger cysts were multilocular. At the angle between the "healed" focal dissection, just above the right coronary cusp, and the thin remaining portion of the aorta, there was abundant proliferation of fibroblasts. Much of the fibrous connective tissue here had undergone hyaline degeneration.

The myocardium showed the changes typical of marked hypertrophy. There were no areas of severe scarring. The coronary vessels showed only general dilatation. The cystic medionecrosis of the aorta stopped abruptly at the orifices of these vessels. No severe changes of an arteriosclerotic nature were present. No perivascular cellular infiltrations were detected.

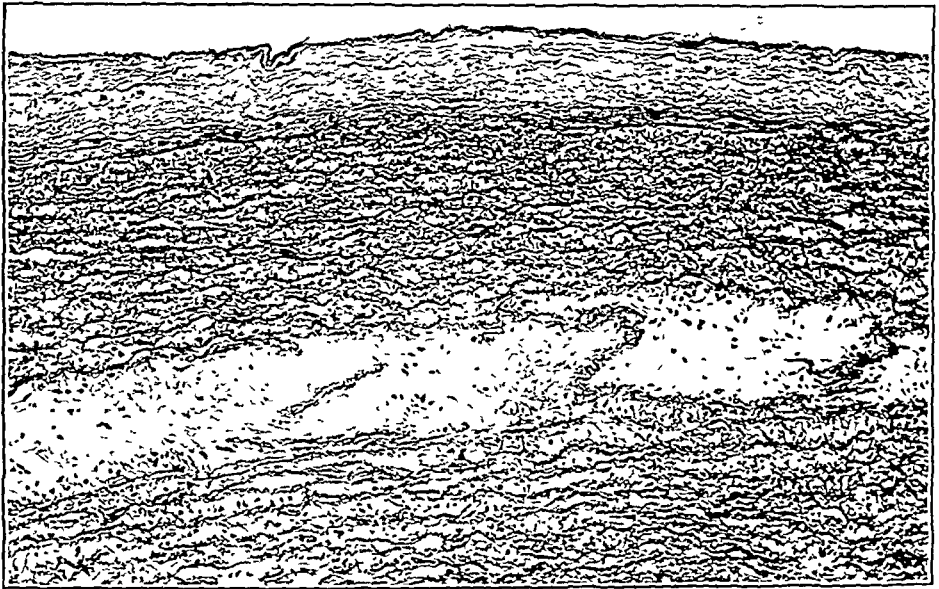


Fig. 6.—Photomicrograph showing high-power detail of a portion of the area in Fig. 5. Van Gieson connective tissue stain. Magnification, 117 diameters.

A great many sections of aorta, heart, and other organs were studied by modifications of the Warthin-Starry technique for spirochetes, with known, positive material as a control. No spirochetes or suggestive structures were seen in any section.

DISCUSSION

An attempt to correlate the sequence of clinical and pathologic events in this case is of great interest, although, of course, speculative. The onset of the dissection resulting in the transverse shelf just above the aortic ring was probably marked by the sudden attack in February, 1934. At that time, examination disclosed the usual manifesta-

tions of severe aortic regurgitation, plus an intense, rough, systolic aortic thrill and murmur suggesting a bizarre valvular deformity or ruptured aortic cusp. Many examinations previously had revealed no such abnormalities. The dating of the dissection at some remote time is justified by the fact that the transverse fold was covered with endothelium. Arrest of the dissection at that time, with "healing," prevented the rupture and death which occur within a relatively short time in more than 90 per cent of cases of dissecting aneurysm.^{12, 15} The pain in the right lower chest was caused by infarction of the lung. The retrosternal and precordial pain in December, 1936, was probably the result of the tearing and elevation of the intima and part of the media in the other transverse tears in the ascending aorta. The extremely severe pain in the lumbar region after Dec. 31, 1936, was no doubt caused by the tears and beginning dissections in the abdominal aorta.

The prominent transverse projection into the lumen of the ascending aorta accounted for the peculiar physical findings, especially the systolic thrill and murmur, suggesting a ruptured aortic cusp. In retrospect, the pulse pressure curves in this case (Fig. 2) may be interpreted as suggesting a widely dilated aortic ring with, however, intact valve cusps, and, together with the aortic sound tracing, may be useful in differentiating pure aortic insufficiency or stenosis from a condition such as was present in this case. In view of the generalized weakening of the aortic media, it is quite likely that the insufficiency was due to relaxation of the musculature supporting the aortic ring, as suggested by Anders.¹⁶ Occurrence of the signs of aortic insufficiency in the presence of normal aortic valve cusps has been mentioned before, in reports dealing with dissecting aneurysms, by Resnick and Keefer,¹⁷ Borger,¹⁸ Busse,¹⁹ Letulle,²⁰ and Moreau.²¹

Most patients with dissecting aneurysm who have survived the initial attack have also developed greatly enlarged hearts within a relatively short time, and have died sooner or later from myocardial failure, if not from rupture of the partially destroyed aortic wall. Although the occurrence of this myocardial hypertrophy and failure has been recognized since the thorough reviews long ago by Peacock²² and Moosberger,²³ no satisfactory explanation has yet been developed. In some cases, the dissection has established a large artificial lumen, or communication with a vein, resulting in failure as in arteriovenous aneurysm.²⁴

As indicated in the descriptive name given to this disease by Erdheim, the etiology is entirely unknown. The theories closely resemble those proposed for dissecting aneurysm and for spontaneous aortic rupture, for which conditions it is probably the cause. Most of the reported cases occurred in middle-aged men with hypertension, in whom arteriosclerotic changes were usually not any more advanced than was consistent with the patient's age. On the other hand, quite a number

of cases have been in young individuals between the ages of 20 and 35 years. Marked hypertension of considerable duration has been found in practically all reported cases of Erdheim's disease in which the patient was studied prior to the development of symptoms. However, in the case reported here, the blood pressure was always within the normal range on frequent examinations prior to the finding of the very large pulse pressure of fully developed aortic insufficiency on the day after the sudden onset of the cardiac illness. Shennan²⁸ found, in his analysis of all reported cases of dissecting aneurysm, that many of the patients were known to have had normal blood pressures.

So-called "spontaneous" rupture of the ascending aorta has been reported^{11, 25, 26} in three young women, 22, 23, and 30 years of age, respectively, all of whom were in the last months of pregnancy. In all three the typical cystic medionecrosis of the aortic wall, as described by Erdheim, was found to be the cause of the rupture. The 30-year-old patient of Gobel²⁵ was known to have had "essential hypertension," with a blood pressure of 145/95, eight years earlier, and died suddenly during an attack of eclampsia. The other two gave no history of disease. Gobel collected eight previously reported cases of spontaneous rupture of the ascending aorta during the last months of pregnancy in young women 26 to 35 years of age; although histologic study was inadequate in these cases, it is probable that the cause was cystic medionecrosis. The significance of this occurrence during pregnancy is unknown, but the early age of the patients is most striking.

It is hazardous to designate any lesion as "idiopathic" when there is a known history of syphilis, in view of the well-known protean manifestations of that disease. However, it does not seem probable that syphilis could be the cause of the disease described by Erdheim, for of all of the twenty-seven cases already reported, in only two was there any clinical or pathologic suspicion of syphilis. This patient began his antisyphilitic therapy within a month after the initial infection, and followed the prescribed course of treatment for over three years; his serologic tests became negative early and remained so. It is believed that his antisyphilitic therapy was adequate and that syphilis probably played no etiologic role in his disease.

Some authors, including Osler²⁷ and Shennan,²⁸ suggest that possibly syphilis may play some role in causing dissecting aneurysms. On the other hand, Loeschke²⁹ and Gager³⁰ believed that the proliferative reaction of syphilis has a binding effect on the layers of the media which tends to prevent the formation of dissecting aneurysms in syphilitics. However, the consensus of recent writers seems to be that syphilis neither predisposes to, nor prevents, dissecting aneurysms. Shennan²⁸ especially stresses this in his excellent review of 300 accepted cases taken from the literature, in only thirteen of which was there any clinical or pathologic evidence of syphilis.

More important is the possibility that Erdheim's idiopathic medionecrosis cystica is due to some unknown substance, such as endocrine or infectious products, or drugs. This case is the only one reported in which there was any prolonged treatment with drugs.

Likewise, it is improbable that heavy physical exertion causes either the disease or the dissecting aneurysms with which it is so often associated. Although strain or trauma is frequently associated with the acute onset of symptoms, the underlying pathologic changes have undoubtedly developed earlier. The early stages in the pathogenesis of cystic medionecrosis are unknown, for only cases in which the lesions were advanced and resulted in fatal rupture of the aorta have been recognized.

It is very important to stress the pathogenic significance of medionecrosis aortae idiopathica cystica in dissecting aneurysms. In all of the twenty-eight cases reported, this lesion resulted in death from ruptured dissecting aneurysm. The histologic descriptions and illustrations in Shennan's monograph²⁸ suggest that in at least seven of his seventeen cases of dissecting aneurysm there were present the typical changes of Erdheim's cystic medionecrosis. The histologic descriptions of "dissecting arteriitis or mesaortitis," made long ago by Babes and Mironescu³⁴ and by Whitman and Stein,³⁵ suggest that their two cases of dissecting aneurysm were also examples of the idiopathic cystic medionecrosis described by Erdheim; no doubt the literature contains other isolated cases which, if they had been studied more carefully histologically, could have been included in this group. Unfortunately, very few of the hundreds of reports on dissecting aneurysms have included adequate histologic descriptions. It is not impossible that dissection of the media might be due occasionally to definite changes in the aorta associated with arteriosclerosis, syphilis, or points of "lowered resistance." Such points of "lowered resistance" may exist at the insertion of the atrophied ductus arteriosus, as stressed by Peery.^{31, 32} In thirteen of his 300 collected cases, Shennan²⁸ described changes in the aortic wall, due to congenital stenosis or occlusion of the isthmus, which had led to rupture and dissection in the media. However, it seems certain that the most important underlying lesion in cases of dissecting aneurysm is this idiopathic cystic medionecrosis which has been so generally overlooked. Recognition of this disease process should result in its more frequent diagnosis, especially in patients with dissecting aneurysm who come to autopsy.

The association of cystic medionecrosis and dissecting aneurysm should be considered in the differential diagnosis when patients complain of sudden, severe, tearing, or stabbing pain in the chest, especially if there is also pain in the back, or pain radiating into the legs or arms. The differential diagnosis of dissecting aneurysm should not be too difficult if the possibility is only borne in mind. It is usually not suspected.

The most common errors in diagnosis are to mistake it for coronary occlusion, angina pectoris, syphilitic aneurysm, pulmonary embolism, or rupture of an aortic cusp. The recent excellent papers of Shennan,²⁸ Osgood,¹³ Glendy,¹⁰ McGeachy,¹⁴ et al., should stimulate clinical acuity in the diagnosis of dissecting aneurysm; Wood and his associates¹² have given special consideration to its roentgenographic features.

In cases in which dissecting aneurysm of the ascending aorta has been thought of, the sudden development of a very intense systolic thrill and murmur over the aortic area, in addition to the aortic diastolic murmur and other signs of aortic regurgitation, should be enough to suggest the possibility that there is an abnormal transverse shelf of dissected media, such as occurred in this case. Rupture of an aortic valve cusp will be very difficult to differentiate; the clinical features of this condition were admirably reviewed by Howard,³⁶ and more recently by Kissane, Koons, and Fidler.³⁷ Likewise, the possibility that aortic stenosis may be combined with the insufficiency must be excluded on the basis of history, pulse pressure measurements and tracings, and roentgenologic features.

Treatment should be directed mainly toward relief of the pain of the acute attack and prevention of any exertion that might tend to raise the blood pressure. Later, venesection and the administration of nitrites have been suggested. No benefit is to be expected from any known surgical operation.

The prognosis in cases of dissecting aneurysm is very grave. For that reason its diagnosis is of great importance, especially because of the more cheering results promised by the modern treatment of coronary occlusion, with which it is most likely to be confused. In the majority of reported cases the patients have died within a period of a few hours or days, although a few have survived for longer periods. Very rarely, indeed, the dissection may become arrested, with more or less complete healing, such as probably occurred in this case, with much longer duration of life. Ultimately, however, complete rupture of the vessel wall or myocardial failure will result in death. At present no method is known of recognizing the changes preceding dissecting aneurysm prior to the acute onset of symptoms. If such recognition were possible, no specific or arresting therapy is known.

CONCLUSION

1. This is the twenty-eighth case to be reported in which there were the typical changes of *medionecrosis aortae idiopathica cystica*, as described by Erdheim; in all of them, this disease was the pathogenic basis for ruptured dissecting aneurysm.

2. The cystic medionecrosis had caused several, small, dissecting aneurysms of the aorta. One of these had ruptured, causing death. Another had evidently formed about three years before death; healing

of this had produced a prominent transverse ridge in the ascending aorta, resembling a semilunar cusp, and giving rise to peculiar physical signs.

3. The ante-mortem diagnosis of dissecting aneurysm, with the associated pathologic picture of Erdheim's cystic medionecrosis, should be made more often than it is. The diagnosis of this condition warrants a grave prognosis.

For permission to report this case and helpful suggestions, I am indebted to Prof. J. T. Wearn, Prof. H. T. Karsner, Dr. A. R. Moritz, Dr. J. M. Hayman, Jr., and Dr. H. N. Feil. The autopsy was performed by Dr. Joseph Kahn.

REFERENCES

1. Erdheim, J.: Medionecrosis aortae idiopathica, *Virchows Arch. f. path. Anat.* 273: 454, 1929.
2. Erdheim, J.: Medionecrosis aortae idiopathica cystica, *Virchows Arch. f. path. Anat.* 276: 187, 1930.
3. Moritz, A. R.: Medionecrosis aortae idiopathica cystica, *Am. J. Path.* 8: 717, 1932.
4. Gsell, O.: Wandnekrosen der Aorta als selbständige Erkrankung und ihre Beziehung zur Spontanruptur, *Virchows Arch. f. path. Anat.*, 270: 1, 1928.
5. Cellina, M.: Sulle "rottture cosiddette spontanee" del aorta ad in particolare su di una rara alterazione dell tunica media del vaso, *Arch. ital. di anat. e istol. pat.* 2: 1105, 1931.
6. Cellina, M.: Medionecrosis disseminata aortae, *Virchows Arch. f. path. Anat.* 280: 65, 1931.
7. Levinson, B.: Ueber tödliche Aortenzerreissung aus geringen Ursachen, *Virchows Arch. f. path. Anat.* 282: 1, 1931.
8. Neuburger, K.: Ueber Aortenveränderungen bei Spontanruptur, besonders über die mucoid-zystische Entartung der Aortenmedia, *Ztschr. f. Kreislaufforsch.* 24: 169, 1932.
9. Orsos-Debreceen, F.: Die Struktur der Aorta ascendens und ihre pathologische Bedeutung, *Verhandl. d. deutsch. path. Gesellsch.* 26: 365, 1931.
10. Glendy, R. E., Castleman, B., and White, P. D.: Dissecting Aneurysm of the Aorta; Clinical and Anatomical Analysis of Nineteen Cases, Thirteen Acute, With Notes on Differential Diagnosis, *AM. HEART J.* 13: 129, 1937.
11. Klotz, O., and Simpson, W.: Spontaneous Rupture of the Aorta, *Am. J. M. Sc.* 184: 455, 1932.
12. Wood, F. C., Pendergrass, E. P., and Ostrum, H. W.: Dissecting Aneurysm of the Aorta; With Special Reference to Its Roentgenographic Features, *Am. J. Roentgenol.* 28: 437, 1932.
13. Osgood, E. E., Gourley, M. F., and Baker, R. L.: Diagnosis of Dissecting Aneurysm of the Aorta, *Ann. Int. Med.* 9: 1398, 1936.
14. McGeachy, T. E., and Paullin, J. E.: Dissecting Aneurysm of the Aorta, *J. A. M. A.* 108: 1690, 1937.
15. Kellogg, F., and Heald, A. H.: Dissecting Aneurysm of the Aorta; Report of Case Diagnosed During Life, With Pathologic Study, *J. A. M. A.* 100: 1157, 1933.
16. Anders, J. A.: Relative Aortic Incompetency of Muscular Origin, *Bull. Johns Hopkins Hosp.* 20: 205, 1909.
17. Resnick, W. H., and Keefer, C. S.: Dissecting Aneurysm with Signs of Aortic Insufficiency; Report of Case in Which Aortic Valves Were Normal, *J. A. M. A.* 85: 422, 1925.
18. Borger, H.: Ueber einen Fall von geheiltem Aneurysma dissecans der Aorta, *Ztschr. f. klin. Med.* 58: 282, 1906.
19. Busse, O.: Ueber Zerreibungen und traumatische Aneurysmen der Aorta, *Virchows Arch. f. path. Anat.* 183: 440, 1906.
20. Letulle, M.: Aneurysme dissequant étendu à la totalité de l'aorte et spontanément guéri; signes d'insuffisance aortique avec intégrité parfaite des valvules sigmoïdes, *Bull. et mém. Soc. méd. d. hôp. de Paris* 22: 1045, 1905.

21. Moreau, E.: Contribution a l'etude des aneurysmes dissequants de la crosse de l'aorte, Paris, 1907.
22. Peacock, T. B.: Report on Cases of Dissecting Aneurism, Tr. Path. Society of London 14: 87, 1863.
23. Moosberger, W.: Zur Symptomatologie des Aneurysma dissecans, Schweiz. med. Wehnschr. 54: 325, 1924.
24. Lewis, T., and Drury, A. N.: Observations Relating to Arteriovenous Aneurism: Circulatory Manifestations in Clinical Cases with Particular Reference to Arterial Phenomena of Aortic Regurgitation, Heart 10: 301, 1923.
25. Gobel, A.: Spontanruptur der Aorta bei einer Schwangerin im 8. Monat auf dem Boden degenerativer Mediaveränderungen der Aorta ascendens, Zentralbl. f. Gynäk. 60: 38, 1936.
26. Milew, L.: Spontanruptur der Aorta im letzten Schwangerschaftsmonat, Zentralbl. f. Gynäk. 60: 2912, 1936.
27. Osler, W., and McCrae, T.: Modern Medicine, Philadelphia, 1915, Lea and Febiger, 4: 467.
28. Shennan, T.: Dissecting Aneurisms, Medical Research Council Monograph, special report series, No. 193, London, 1934. Published by His Majesty's Stationery Office.
29. Loeschke, A.: Aneurysma dissecans auf luetischer Grundlage, Frankfurt Ztschr. f. Path. 36: 56, 1928.
30. Gager, L. T.: The Symptoms of Dissecting Aneurysms of the Aorta, Ann. Int. Med. 2: 658, 1929.
31. Peery, T. M.: Dissecting Aneurisms, With Report of 5 Cases, AM. HEART. J. 12: 650, 1936.
32. Peery, T. M.: "Healed" Dissecting Aneurism, Arch. Path. 21: 647, 1936.
33. White, P. D.: Heart Disease, 2nd ed., New York, 1937, The Macmillan Co., pp. 490, 510.
34. Babes, V., and Mironescu, T.: Ueber dissezierende Arteriitis und Aneurysma dissecans, Beitr. z. path. Anat. u. z. allg. Path. 48: 221, 1910.
35. Whitman, R. G., and Stein, H. B.: A Contribution to the Pathogenesis of Dissecting Aneurisms: A Case of Dissecting Mesoarthritis (Babes and Mironescu) Without Dissecting Aneurism, J. Med. Research 44: 579, 1924.
36. Howard, C. P.: Aortic Insufficiency Due to Rupture by Strain of a Normal Aortic Valve, Canad. M. A. J. 19: 12, 1928.
37. Kissane, R. W., Koons, R. A., and Fidler, R. S.: Traumatic Rupture of Normal Aortic Valve, AM. HEART J. 12: 231, 1936.

THE EFFECTS OF DIPHTHERIA TOXIN UPON THE HEART*

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CARDIAC failure during, or following, the acute stage of diphtheria is not uncommon. Surprisingly, death from this cause is frequently not entirely explained by the pathologic changes in the heart. This subject has been studied repeatedly during the past thirty-odd years (Warthin,¹ 1924). The lesions generally described are (grossly) dilatation of the right-sided chambers, flabbiness, friability, greyness, opacity, and tigroid mottling of the myocardium, and (microscopically) interstitial edema, congestion, leucocytic infiltration, and alteration of the fibers, such as loss of cross striations, hyaline degeneration, granularity, vacuolization, and even necrosis. There appears to be no selective action on the conducting system. The frequent paucity, or even absence, of cardiac lesions, contrasted with the dramatic collapse in diphtheria, has led some authors to look elsewhere for the cause of death, or to hypothesize a functional alteration of the myocardium. With this last phase of diphtheria intoxication we are chiefly concerned.

Disorders in conduction were early noted. Huguenin² (1890) first observed heart block. Alsleben³ (1909), by graphic registration, demonstrated complete A-V dissociation, and this was confirmed electrocardiographically in 1913 by Röhmer.⁴ Little has been added to these facts. In a recent summary of their observations on electrocardiographic changes in such hearts, Burkhardt and his associates⁵ (1938) describe: (a) alterations of the T wave which may vary from a slight depression of the S-T line to inversion, a diphasic form, or complete extinction of the T wave; and (b) various degrees of conduction changes, varying from prolongation of QRS to complete A-V dissociation. They observed no deaths in cases in which alterations of the T wave were the sole electrocardiographic disturbance but did note that conduction changes were of grave prognostic significance. McCulloch (1920) stated that in cases in which there were profound disturbances in conduction the outcome was usually fatal. He expressed the opinion that "recovery in these cases depends upon the ability of the heart to preserve a cardiac reserve sufficient for the need of the patient" and that "cardiac failure results when this reserve is used up." Cardiac reserve is a difficult thing to put into terms more specific than "the capacity of the heart to do work." McCallum⁶ (1914), in an experimental study upon dogs, found that the actual amount of work done by the diphtheria-poisoned heart was as great as that done by the normal heart, and he concluded that death occurring during the height of an attack of diph-

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*Research Paper 519, Journal Series, University of Arkansas.

Received for publication Feb. 8, 1939.

theria is not necessarily exclusively the result of a direct injury to the heart. If we define cardiac reserve in terms of physiologic extensibility of the heart's fibers, it is conceivable that the heart, as described by McCallum, may be performing its work, yet be extremely close to the physiologic limits of dilatation.

The extent and the mechanism by which glycogen contributes to the cardiac reserve are not inarguable matters. Neither is the behavior of cardiac glycogen during the course of an acute diphtheritic infection a matter upon which everyone agrees. Experimentally, the results of studying the action of the toxin upon the heart have varied widely with different workers. Using a carmine staining method, Grunke and Kampf⁷ (1933) studied the hearts of guinea pigs which had been injected with diphtheria toxin. They reported that in guinea pigs which had been given sufficient diphtheria toxin to produce death in 14 to 17.5 hours no essential alteration of the glycogen content of the heart occurred, while in animals which had received doses of toxin sufficient to produce death in 168 to 273 hours the ventricles and the septum were found to be free of glycogen, and the glycogen content of the atria was notably reduced, as compared to the normal atria. It is worthy of note that the animals given the slowly lethal dose frequently died in convulsions. In contrast to the action of the toxin upon the glycogen stores of the heart, they pointed out that the hearts of guinea pigs starved for a period of 100 hours were rich in glycogen.

Using a colorimetric method, v. Kiss and Kulesar⁸ (1934) obtained results considerably different from those just described. Guinea pigs which had been given enough toxin to produce death in 20 to 22 hours showed an average increase in the glycogen content of the whole heart of 36 per cent over that of the controls. Skeletal muscle glycogen and blood sugar showed parallel rises; liver glycogen did not share in this rise.

Grunke and his co-workers⁹ (1938), using a chemical method, reinvestigated the glycogen content of the hearts of guinea pigs and white rats. They interpreted their results as showing an increased glycogen content of the hearts as a result of small and repeated doses of diphtheria toxin. The greatest rise obtained, however, was to an average of 441 ± 61 mg. per cent from a normal level of 370 ± 43 mg. per cent, whereas in guinea pigs which had been starved for 24 hours and 72 hours the averages rose to 475 ± 14 mg. per cent and 554 ± 26 mg. per cent, respectively.

We have deemed it worth while to study by a chemical method the glycogen distribution in the hearts of dogs injected with diphtheria toxin, and to attempt to correlate this with the electrocardiographic and pathologic findings in these hearts.

METHODS

Dogs free of disease were placed upon a basic diet which was complete in so far as the known food requirements are concerned and kept a sufficiently long time to

establish a normal heart rate, as shown electrocardiographically. They were then injected subcutaneously with diphtheria toxin* in doses varying from 1.8 M. L. D. to 8.1 M. L. D. per kilogram of body weight. (M. L. D. refers to the minimum lethal dose for a guinea pig.) Electrocardiographic records were made daily. At such time as either recovery or death appeared imminent, the animal was selected for a study of his cardiac glycogen. Analyses of the various parts of the heart for glycogen were conducted exactly as outlined in our preceding papers (Boyle and McDonald,¹⁰ 1938; McDonald, Boyle, and DeGroat,¹¹ 1938). The method is a modification of Pflüger's method.

RESULTS

Tables I, II, and III summarize the results obtained:

TABLE I

GLYCOGEN DISTRIBUTION IN THE HEARTS OF NORMAL DOGS (MG. PER GM. OF TISSUE, CALCULATED AS GLUCOSE)

NO.	ATRIA		VENTRICLES		SEPTUM
	RIGHT	LEFT	RIGHT	LEFT	
N-1	4.4	5.5	6.9	4.2	6.6
N-2	6.6	9.3	10.4	6.7	7.1
N-3	5.6	6.8	7.7	6.5	5.9
N-4	6.1	7.4	6.9	5.7	4.8
N-5	5.9	7.4	6.9	7.5	7.1
N-6	5.2	5.5	5.8	4.3	4.7
Avg.	5.7	6.9	7.4	5.8	6.0

*Furnished through the courtesy of Eli Lilly and Company.

TABLE II

GLYCOGEN DISTRIBUTION, ELECTROCARDIOGRAPHIC BEHAVIOR, AND PATHOLOGIC FINDINGS IN THE HEARTS OF DOGS GIVEN A QUICKLY LETHAL DOSAGE OF DIPHTHERIA TOXIN. (GLYCOGEN CALCULATED AS IN TABLE I)

NO.	HOURS DURAT.	ELECTROCARDIO- GRAPHIC BEHAVIOR	GLYCOGEN DISTRIBUT.				SEPT.	PATHOLOGIC FINDINGS
			ATRIA		VENTRIC.			
			RT.	LT.	RT.	LT.		
1-D	20	A-V Rhythm	6.8	7.7	7.8	6.9	5.3	Parenchym. Degen.
3-D	21	Depressed S-T	6.1	8.1	9.3	8.2	7.1	Parenchym. Degen.
6-A	23	Depressed S-T	4.0	6.9	4.4	4.1	4.3	Parenchym. Degen.
		Average Glycogen	5.6	7.6	7.2	6.4	5.6	

TABLE III

GLYCOGEN DISTRIBUTION, ELECTROCARDIOGRAPHIC BEHAVIOR, AND PATHOLOGIC FINDINGS IN THE HEARTS OF DOGS GIVEN A SLOWLY LETHAL DOSAGE OF DIPHTHERIA TOXIN. (GLYCOGEN CALCULATED AS IN TABLE I)

NO.	HOURS DURAT.	ELECTROCARDIO- GRAPHIC BEHAVIOR	GLYCOGEN DISTRIBUT.				SEPT.	PATHOLOGIC FINDINGS
			ATRIA		VENTRIC.			
			RT.	LT.	RT.	LT.		
2-D	88	Partial A-V block, 4:1	6.7	10.8	9.4	6.7	6.2	Parenchym. Degen.
5-D	89	Dep. and Notch. S-T	5.3	7.3	8.9	8.8	9.7	Parenchym. Degen.
6-D	89	Long P-R; Dep. S-T	6.2	9.2	8.3	6.9	6.8	Parenchym. Degen.
		Average Glycogen	6.1	8.8	8.7	7.4	7.6	

DISCUSSION

The electrocardiographic changes noted in this series are chiefly of the nature of block. The degree of block varied from a simple lengthen-

ing of the P-R interval to assumption of the pacemaker's role by the ventricular bundle. Partial A-V block in a ratio of 4:1 appeared once. The depressing, sloping, and notching of the S-T segment would suggest at least functional damage to the myocardium. The T wave was frequently diphasic, notched, or opposite in phase to the T wave which was normal for the particular dog. In one case the direction of the T wave was frequently positive, frequently negative.

The term "parenchymatous degeneration" is employed in the above tables to designate such changes as granularity of the fibers, loss of cross striations, streaks of hyaline, and swelling or shrinking of the nuclei. These changes were not general for the whole heart nor general in its several parts. The magnitude of the changes was small. If seen in a routine autopsy, they would attract little attention. Worthy of note were the streaks of hyaline in scattered muscle fibers, which offered the nearest approach to a characteristic pathologic alteration. Each of the following abnormalities was seen once: subendocardial edema, sparse monocytic infiltration, and endothelial (endocardial) proliferation. The survival time of the animals, up to 89 hours, did not appreciably alter the findings.

Analysis of these hearts for glycogen disclosed no striking alterations in either distribution or total content. Examination of all parts of the hearts of dogs which had been given a quickly lethal dose of the toxin showed a quite normal distribution. In those animals which were given a slowly lethal dose, averages show a 10 to 20 per cent rise in the atria and the left ventricle, no change in the septum, and a 7 per cent loss in the right ventricle. Considered on the basis of the whole heart for all the dogs given such a dose, a 10 per cent rise occurred. When we note the marked increase in cardiac glycogen during starvation, as described by Grunke and his co-workers, and consider that our dogs starved for three days because they refused to eat, we regard this rise as insignificant and probably due to this starvation, rather than to any specific effect of the diphtheria toxin upon cardiac glycogen.

Mindful of the fact that many cardiac failures associated with diphtheria occur several days after the height of the infection, we injected sixteen animals with a smaller dose than that administered to dogs when we were seeking a delayed death. After these dogs appeared to be recovering from the initial dose, we administered a second, and sometimes a third, dose, smaller in amount than the initial dose. Death resulted in fifteen of these sixteen cases. The one survivor, which had been given $\frac{1}{2}$ M. L. D. on the first day, another $\frac{1}{2}$ M. L. D. on the fourth day, and $\frac{1}{8}$ M. L. D. on the eighth day, was studied on the eleventh day. His cardiac glycogen was well within the limits of normal, and his heart displayed no changes different from those previously described for this series.

It is interesting to compare the behavior of cardiac glycogen in these cases of severe diphtheritic toxemia with that in severe hyperthyroidism,

which sometimes terminates in equally dramatic heart failure. In the former there is a moderate increase, while in the latter there is a definite decrease. There is little evidence, we believe, that the cardiac failure in either event is primarily contingent upon a disturbance of glycogen metabolism.

SUMMARY

1. The hearts of seven dogs which had been given varying doses of diphtheria toxin were studied with respect to electrocardiographic behavior, glycogen distribution, and pathologic changes.

2. The electrocardiographic changes noted consisted of various degrees of block and abnormalities of the T wave.

3. Parenchymatous degeneration of a mild degree was invariably present. The most characteristic change was the presence of hyaline streaks scattered through the muscle fibers.

4. Glycogen, taking the heart as a whole, showed a 10 per cent rise in the hearts of dogs given a slowly lethal injection of diphtheria toxin. A rise was noted in the two atria and the two ventricles, and no change in the septum. A quickly lethal dose failed to produce any effects upon cardiac glycogen.

5. In view of the increases in cardiac glycogen which occur during starvation, and of the self-imposed starvation (anorexia) always present in severe diphtheritic toxemia, it is suggested that the moderate rise encountered in such cases is the result of starvation, rather than of any specific effect of the diphtheria toxin upon cardiac glycogen.

The authors desire to thank Mr. J. R. Carter for much technical assistance.

REFERENCES

1. Warthin, S. J.: The Myocardial Lesions of Diphtheria, *J. Infect. Dis.* 35: 32, 1924.
2. Huguenin: Thèse de Paris, 1890 (Cited by H. Vaquez).
3. Alsleben, M.: (Cited by H. Vaquez.) *Ztschr. f. klin. Med.* Bd. 66A: 1, 1909.
4. Röhmer: (Cited by H. Vaquez.) *Jahrbuch f. Kinderheilk.* 26: 391, 1913.
5. Burkhardt, E. A., Eggleston, C., and Smith, L. W.: Electrocardiographical Changes and Peripheral Nerve Palsies in Toxic Diphtheria, *Am. J. Med. Sc.* 195: 301, 1938.
6. McCallum, W. G.: The Mechanism of Circulatory Failure in Diphtheria, *Am. J. Med. Sc.* 147: 37, 1914.
7. Grunke, W., and Kampf, Hans: Glycogen Content of Heart Muscle After Administration of Diphtheria Toxin, *Ztschr. f. d. gesamt. exp. Med.* 91: 471, 1933.
8. v. Kiss, P., and Kulcsar, M.: The Alteration of the Carbohydrate Content of Heart Muscle by the Action of Diphtheria Toxin, *Ztschr. f. Kinderheilk.* 56: 465, 1934.
9. Grunke, W., Schumann, H., and Böhn, H.: Concerning the Alteration of the Glycogen in the Hearts of Diphtheria Poisoned Animals, *Ztschr. f. Kinderheilk.* 103: 117, 1938.
10. Boyle, Robt. W., and McDonald, C. H.: The Glycogen Content of the Normal Heart, *Proc. Soc. Exp. Biol. and Med.* 39: 14, 1938.
11. McDonald, C. H., Boyle, R. W., and DeGroat, A. F.: Hyperthyroidism and Cardiac Glycogen, *Am. J. Physiol.* 124: 742, 1938.

THE EFFECT OF CARBON DIOXIDE INHALATION ON THE PERIPHERAL BLOOD FLOW IN THE NORMAL AND IN THE SYMPATHECTOMIZED PATIENT

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THE blood flow in the human hand under the influence of various oxygen and carbon dioxide concentrations has been investigated by Gellhorn and Steck,¹ who found that carbon dioxide regularly induced a diminution of the blood flow during the period of inhalation of this gas, and that on readmission of air the blood flow returned to the original level. In contradistinction to the uniformity of these results, it may be said that the influence of various oxygen concentrations on the blood flow is more variable. In general, they found that with increasing severity of the oxygen want the blood flow through the hand decreased, and this was followed on readmission of air by a marked compensatory phase in which the blood flow was greatly increased. In more moderate degrees of oxygen deficiency, induced by inhalation of oxygen-nitrogen gas mixtures containing about 10 per cent oxygen, the opposite picture predominated. Greatly increased blood flow during the period of anoxia was followed by a gradual return to normal on readmission of air.

The results may be explained as follows. Three factors appear essential in determining the blood flow through the hand under the experimental conditions mentioned above:

1. The first is the influence of carbon dioxide excess and oxygen deficiency on the vasomotor center. According to the investigations of Lambert and Gellhorn,² the inhalation of carbon dioxide increases the vasomotor tonus by direct stimulation of the vasomotor center and by reflex stimulation of this center through the chemoreceptors in the carotid and aortic bodies. Oxygen deficiency also increases the vasomotor tonus, but this is due solely to reflex stimulation of the carotid and aortic bodies, for after their removal the blood pressure decreases on inhalation of oxygen-deficient gas mixtures, whereas an increase occurs regularly as long as the peripheral chemoreceptors are intact.

2. The peripheral effect of oxygen deficiency and of carbon dioxide excess on the blood vessels consists in dilatation of the blood vessels (Fleisch, Sibul, and Ponomarev,³ 1932), (Hermann, Morin, and Vial,⁴ 1936, and others), and is therefore opposed to the central effects of these gases as described under 1.

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Aided by a grant from The John and Mary R. Markle Foundation.

Received for publication Feb. 8, 1939.

3. The metabolism of the tissues is to be considered. When the oxygen supply to the tissues is temporarily diminished, either because the blood supply is diminished or interrupted, or because the amount of oxygen carried by the blood and delivered to the tissues per unit of time is lessened, metabolites* are formed which bring about a dilatation of the blood vessels. This leads to an increased oxygen supply to the tissues and to the disappearance of these metabolites. The formation of metabolites seems to be responsible for the appearance of the compensatory phase after readmission of air. Although under the influence of carbon dioxide the blood vessels are constricted and the amount of blood flowing through the tissues is greatly reduced, the typical effects of oxygen deficiency in the tissues are absent. No compensatory phase occurs. This is due to the fact that carbon dioxide not only reduces the blood flow through the tissues but also reduces their metabolism (Rein⁵).

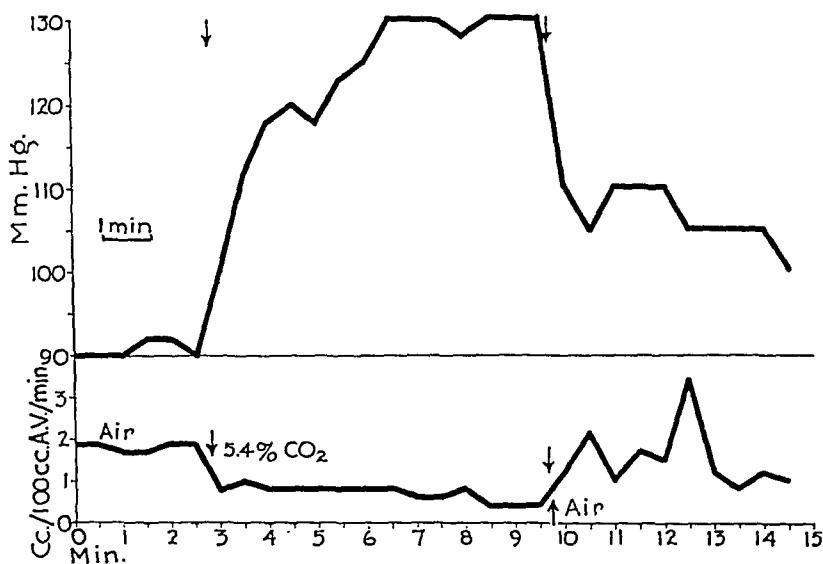


Fig. 1.—Simultaneous recording of blood pressure and blood flow in man, and the effect of the inhalation of 5.4 per cent carbon dioxide.

The absence of this compensatory phase under the conditions of carbon dioxide inhalation makes the circulatory conditions much simpler than in the case of induced oxygen deficiency. After inhalation of suitable concentrations of carbon dioxide (4 to 5.4 per cent), there is only a rivalry between the central nervous impulses originating in the vasomotor center and the peripheral effects of carbon dioxide. Under such conditions it was found regularly that the central effect predominates. Therefore the peripheral blood flow is reduced. This interpretation is

*This term is used advisedly, since the nature of these products is not known at the present time. We know that in the state of acclimatization to high altitude the concentration of lactic acid in the blood is not increased (Edwards, H. T.: *Amer. J. Physiol.* 110: 367, 1936). Moreover, recent experiments of Ingraham and Gellhorn (*Proc. Amer. Physiol. Soc., Toronto, 1939*) have shown that during acute anoxia the tissues (brain, muscle, and blood) become more alkaline, not more acid, and that, at the same time, respiratory activity is greatly increased.

made certain by recording blood pressure and blood flow simultaneously* (Fig. 1). The reduction of blood flow coincides accurately with the period of elevated blood pressure.

This analysis makes it clear that the investigation of the effect of carbon dioxide on the peripheral blood flow is carried out under simpler conditions than the corresponding anoxia experiment. Carbon dioxide appears, therefore, more suitable for the development of a physiologic test which would allow one to decide whether or not sympathetic impulses are present.

METHOD AND MATERIAL

The changes in blood volume were recorded by Freeman's⁶ plethysmographic method. The temperature of the hand was controlled by means of water circulating between an outer and inner cylinder; the water space was one-half inch in diameter. This cylinder was connected to a control tank equipped with an electrothermostat which kept the water bath at a constant temperature. The water was kept circulating by means of a motor. Two inlets were attached near the front end of the cylinder; the outlet was a single hose at the back part of the cylinder.

The outer cylinder was provided with a flanged surface at the front, over which a rubber cuff was stretched and made secure with a ring screw clamp. The rubber cuffs used were of various sizes, depending upon the size of the hand and wrist of the subject. A perfect contact with the wrist as close to the hand as possible was thus obtained. The subject rested for twenty minutes before the hand was placed in the plethysmograph, and from five to ten minutes after the cuff had been applied. The hand volume was recorded by means of a tambour made of fish skin, which was connected to the inner chamber of the plethysmograph. A pressure of 55 to 60 mm. Hg was applied to the arm to occlude the venous return from the hand. The change of volume of the hand was recorded on a kymograph.

After the influence of various oxygen and carbon dioxide concentrations on the peripheral blood flow in normal individuals was determined (Gellhorn and Steckl), additional experiments were carried out on six patients who had undergone bilateral sympathectomy of the hand. The following patients were put at our disposal through the kindness of Dr. G. de Takats.

CASE 1.—M. G., 44 years of age, a white woman, was admitted to the Illinois Research and Educational Hospital Nov. 16, 1937, with the complaint that her fingers and toes became numb when exposed to cold, and that the distal phalanges became white, then dark blue, when she returned to a warm room. The onset was as follows. About five years previous to admission, the patient first noticed that the tips of her fingers became white and numb when exposed to moderately cold weather or cold water. When she warmed the fingers, they turned "black" and felt swollen. This condition became progressively worse. The diagnosis was Raynaud's disease. On Nov. 16, 1937, a "typical"† cervical sympathectomy was performed. On March 1, 1938, peripheral blood flow determinations were begun and continued for several months.‡

*We are greatly indebted to Dr. C. W. Darrow for recording the blood pressure with his apparatus. Cf. Darrow: Continuous Records of Systolic and Diastolic Blood Pressure, *Arch. Neurol. and Psychiat.* 38: 365, 1937.

†In the "typical" cervical sympathectomy the stellate ganglion is removed, and the sympathetic chain is cut below the second dorsal ganglion.

‡This was done in all cases.

CASE 2.—E. F., 38 years of age, a white woman, was admitted to the Illinois Research and Educational Hospital Dec. 27, 1937, with the complaints of pain and numbness of the hands and fingers of two years' duration; pain in the joints and back of one year's duration; and coldness of the hands of two months' duration. The onset was as follows. Two years prior to admission this patient awoke in the morning with numbness in both hands. These attacks recurred at regular intervals throughout the winter, were less frequent through the summer months, then finally subsided, but recurred at a later period. The attacks became more severe when the hands were exposed to cold and were accompanied by cramplike pains in the fingers. The pain was relieved by heat. The symptoms, however, became more frequent and more severe at the time of admission. An attack of numbness and cramplike pains occurred every night. The diagnosis was Raynaud's disease. On Dec. 12, 1937, an "extended"* cervicodorsal sympathectomy was performed on the right side. On May 3, 1938, peripheral blood flow determinations were begun.

CASE 3.—M. M., 44 years of age, a white woman, was admitted to the Illinois Research and Educational Hospital Jan. 31, 1938, with the complaints of bilateral paresthesia and anesthesia of the arms and hands and attacks of pain with whiteness of the extremities. The color later changed to blue and finally became a "beefy" red, which lasted from two to four hours. These attacks were brought on by emotional upsets, and the symptoms were aggravated by cold weather. The onset was as follows. Four years prior to admission the patient first noticed numbness, whiteness, and "beefy" redness of the fingers. The attacks increased in severity and frequency. The diagnosis was Raynaud's disease and neurocirculatory asthenia. On Feb. 1, 1938, a "typical," cervical, incomplete sympathectomy was performed on the right side. On Feb. 8, 1938, an "extended" cervical sympathectomy was performed on the left side. On March 18, 1938, peripheral blood flow determinations were begun.

CASE 4.—M. S., 33 years of age, a white woman, was admitted to the Illinois Research and Educational Hospital, March 14, 1938, with complaints of coldness, pain, tingling, and weakness of the extremities. This condition was aggravated by exposure to cold or by fatigue. The onset was as follows. The patient was well until ten years prior to admission, when she first noticed a gradual onset of pain, which was sharp and sometimes tingling in character, in the upper extremities, particularly on the left side. The pain often started in the right shoulder and radiated to the ulnar side of the arm. Exposure to cold or exertion precipitated it. The diagnosis was Raynaud's disease. On March 22, 1938, an "extended" cervical sympathectomy was done on the left side, followed on Aug. 23, 1938, by an "extended" cervicodorsal sympathectomy. On May 27, 1938, peripheral blood flow determinations were begun.

CASE 5.—D. S., 34 years of age, a colored woman, was admitted to the Illinois Research and Educational Hospital, Feb. 19, 1938, with complaints concerning swelling and coldness of both hands. The onset was as follows. One year prior to admission this patient noticed that her hands were swollen in the morning, and that whenever her hands were exposed to the cold the circulation seemed to stop. The diagnosis was Raynaud's disease. On Feb. 19, 1938, an "extended" cervical sympathectomy was performed on the right side, followed on March 1, 1938, by an "extended" cervical sympathectomy on the left side. On March 21, 1938, peripheral blood flow determinations were begun.

*Dr. de Takats uses the term "extended" cervicodorsal sympathectomy when he removes the third dorsal ganglion in addition to the stellate and second thoracic ganglia. The vertebral artery is also stripped.

RESULTS

The results were uniform and may be illustrated by a typical record (Fig. 2). The vasoconstriction in the hand which had been regularly observed in normal individuals was completely absent. During the inhalation of relatively low concentrations of carbon dioxide (5.4 per cent), there was either no change in blood flow or an increase; whereas, with 6.4 per cent carbon dioxide, the blood flow was regularly increased. On readmission of air the blood flow returned to the normal level. The results indicate clearly that the sympathetic (vasoconstrictor) impulses were absent. When a change in blood flow occurs, it probably is due partially to the effect of increased blood pressure and partially to the peripheral (dilating) action of carbon dioxide.

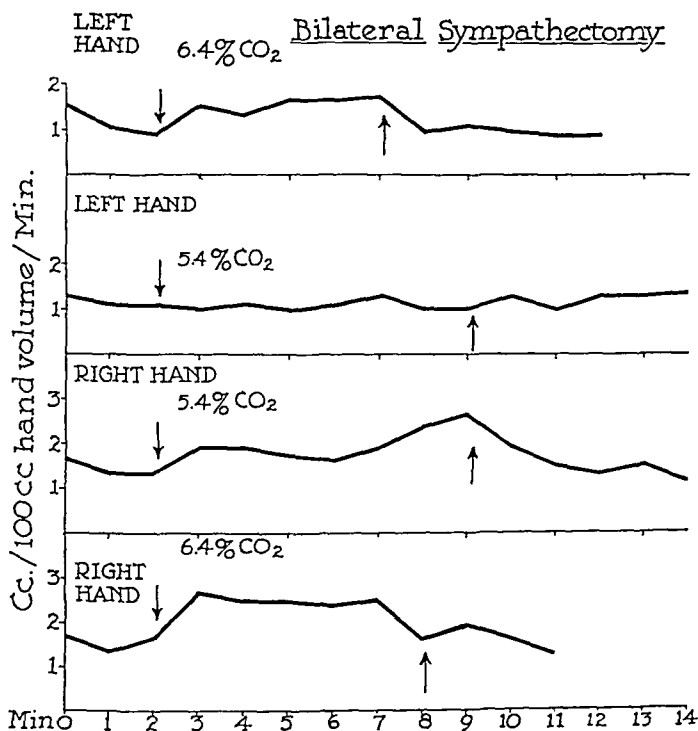


Fig. 2.—The influence of 5.4 per cent and 6.4 per cent carbon dioxide on the blood flow in the sympathectomized hand.

Four of our five patients gave such responses, thus leading to the conclusion that the sympathetic innervation to the hand had been completely removed.

In one case we found, in two out of five experiments with 5.4 per cent carbon dioxide, a distinct reduction in blood flow, which, however, did not persist throughout the whole period of carbon dioxide inhalation. In the other three tests the blood flow remained unchanged. We conclude from these experiments that the sympathectomy in this patient was incomplete.

There was, however, a disagreement between the results obtained with our method and those obtained by clinical observation in regard to one

patient (M. M.). Clinically, she showed some residual sweating in the right hand, but the plethysmograph test showed absence of vasoconstriction during the inhalation of 5.4 per cent carbon dioxide. This seems to indicate that carbon dioxide may have been unable to bring about a vasoconstriction in the hand, even if some sympathetic fibers were still functioning, as shown by the sweating of the hand.* Only further experimentation on a larger number of patients can solve this problem.

The use of oxygen-deficient gas mixtures for similar purposes seems to us, on the basis of numerous experiments, unjustified. As mentioned before,† greatly increased blood flow occurs frequently in normal individuals during oxygen deficiency. Moreover, the experimental subject who responds to a given oxygen-nitrogen gas mixture with a decreased flow, followed (on readmission of air) by a compensatory increased flow, may on another occasion show the opposite type of response. The observation of Freeman, in two cases, that the normal hand showed vasoconstriction and the sympathectomized hand showed vasodilatation under the conditions of oxygen deficiency cannot be considered proof of the absence of sympathetic impulses in the second record, since, according to our experiences, a reversal in vasomotor response to oxygen deficiency may occur even in the normal.

SUMMARY AND CONCLUSIONS

Investigations on the influence of the inhalation of oxygen-deficient gas mixtures and of carbon dioxide in air on the peripheral blood flow in the hand of sympathectomized patients are reported.

It was shown that, whereas carbon dioxide regularly reduces the blood flow in normal persons, this reaction does not occur after sympathectomy. It was then found that with relatively low concentrations of carbon dioxide the blood flow remains unchanged, and that higher concentrations bring about an increased blood flow. This is probably due to the increased blood pressure and dilating action of carbon dioxide on the peripheral blood vessels, which is unopposed by the normally present and increased sympathetic impulses originating in the vasomotor center.

Tests carried out with oxygen-deficient gas mixtures are incapable of determining the presence or absence of sympathetic impulses.

REFERENCES

1. Gellhorn, E., and Steck, I.: The Effect of the Inhalation of Gases With a Low Oxygen and an Increased Carbon Dioxide Tension on the Peripheral Blood Flow in Man, *Am. J. Physiol.* 124: 735, 1938.
2. Lambert, E. H., and Gellhorn, E.: Role of Afferent Nerves in Response of Vasomotor Center to Oxygen Deficiency, *Proc. Soc. Exper. Biol. & Med.* 38: 427, 1938. Cf. also Gellhorn and Lambert: The Vasomotor System in Anoxia and Asphyxia. Contributions to the Adjustment Reactions of the Mammalian Organism. Medical Monographs of the University of Illinois, 1939.

*It may be mentioned that this case is somewhat complicated, inasmuch as a bilateral splanchnicotomy had been carried out on the patient.

†Compare the detailed records in our previous paper.¹

3. Fleisch, A., Sibul, I., and Ponomarev, J.: Über nutritive Kreislaufregulierung; Kohlensäure und Sauerstoffmangel als auslösende Reize, Arch. f. d. ges. Physiol. 230: 814, 1932.
4. Hermann, H., Morin, G., and Vial, J.: Composition gaseuze du sang et appareils vaso-moteurs; action sur les appareils peripheriques; essai de synthese, Ann. de physiol. 12: 255, 1936.
5. Rein, H.: Die Möglichkeit zentralnervöser Regulierung des oxidativen Gesamtstoffwechsels im Warmblüterorganismus durch Kohlensäure, Nahr. Ges. Wiss. Göttingen Math. Physik. Kl. 2: 14, 1936.
6. Freeman, N. E.: Effect of Temperature on Rate of Blood Flow in Normal and Sympathectomized Hand, Am. J. Physiol. 113: 384, 1935. Also Freeman, N. E., Shaw, J. L., and Snyder, J. C.: Peripheral Blood Flow in Surgical Shock; Reduction in Circulation Through Hand Resulting from Pain, Fear, Cold and Asphyxia, With Quantitative Measurements of Volume Flow of Blood in Clinical Cases of Surgical Shock, J. Clin. Investigation 15: 651, 1936.

THE VALUE OF SPECIAL RADIOLOGIC PROCEDURES IN DETECTING CARDIAC ENLARGEMENT IN CHILDREN WITH RHEUMATIC HEART DISEASE*

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THE importance of detecting cardiac enlargement in children with rheumatic heart disease is generally recognized. Without enlargement, the significance of murmurs, especially apical systolic murmurs, often remains doubtful. Marked cardiac enlargement presents no difficulties; it is usually obvious by physical as well as by radiologic examination. It is the detection of slight or moderate cardiac enlargement that is particularly difficult.

In recent years special radiologic procedures have been developed to detect enlargement of the individual chambers of the heart, and new ways of measuring the size of the heart in the anteroposterior position have been devised.

1. *Method for Detecting Enlargement of the Left Ventricle.*

Wilson¹ has been able to detect slight enlargement of the left ventricle by determining the degree of rotation necessary to separate the left lower cardiac border from the vertebral column in the left anterior oblique position. In 97 per cent of 119 normal children, ranging in age from 5 to 15 years, the "angle of clearance" was less than 55 degrees. This author, therefore, concluded that angles of 55 degrees or more were abnormal, indicating left ventricular enlargement. Wilson compared the findings in the normal group with those obtained in children with suspected or definite heart disease. In sixty-four cases of potential heart disease, 76 per cent of the patients showed an angle of clearance of 55 degrees or more. This was interpreted by the author as an indication of cardiac involvement. In 84 per cent of 148 cases of mitral insufficiency the angle of clearance was 55 degrees, or more.

2. *The Detection of Enlargement of the Left Auricle.*

It is generally accepted that slight enlargement of the left auricle can best be detected by observing the course of the barium-filled esophagus in the right anterior oblique position. In order to evaluate the results obtained by this method, it is important to bear in mind the normal variations in the contour of the esophagus. The relation of the esophagus to the heart and great vessels has been carefully studied by Evans.² This author found that in normal individuals the left auricle produces a slight

*This work was aided by a grant from the Commonwealth Fund.
Received for publication Feb. 27, 1939.

curve, or impression, which varies with body build. The normal auricular curve is usually more marked in pyknic than in asthenic individuals and tends to be more evident in children than in adults. The interpretation of a slight increase in the auricular curve in the right anterior oblique position is therefore particularly difficult in children.

If the enlargement of the left auricle is sufficiently marked, the displacement of the barium-filled esophagus to the right is visible in the anteroposterior position. Very pronounced enlargement of the left auricle can also be seen in the left anterior oblique position. The enlarged auricle extends to the left bronchus, giving it a "pushed-up" appearance, and widening the tracheal angle.

3. *Measurements.*

Various ways of measuring the size of the heart in the frontal plane and correlating the findings with other bodily measurements have been described. The cardiothoracic ratio³ was formerly widely used but is now considered unreliable by most observers. At the present time, the correlation of orthodiagraphic measurements of the frontal area of the heart with height and weight is considered a more satisfactory method. Orthodiagraphy, however, is a difficult procedure in children. Tracings of teleoroentgenograms, though less accurate, have therefore been used by some workers. The formula for predicting the normal frontal area, devised by Hodges, Adams, and Gordon,⁴ is based on 169 teleoroentgenograms of children of various ages. This formula has been reduced to tables for clinical use, and Kurtz⁵ has prepared a nomograph from these figures.

PLAN OF STUDY

The interpretation of apical systolic murmurs in children with rheumatic histories has long been a controversial subject. According to the criteria of the New York Heart Association,⁶ the diagnosis of mitral insufficiency should be made only if, in addition to a constant apical systolic murmur, enlargement of the heart is also present. It was thought of interest to see how often enlargement of the left ventricle could be demonstrated in this type of case by the method described by Wilson.¹ At the same time, the absence or presence of enlargement as ascertained by physical examination and measurement of the frontal area in teleoroentgenograms was noted.

A group of fifty-five rheumatic children with apical systolic murmurs who were receiving convalescent care in this institution was selected. The children ranged in age from 8 to 15 years and were under close observation for long periods of time, varying from six months to more than two years. The temperature and pulse rate were taken three times daily, and leucocyte counts and sedimentation rates were done at frequent intervals. Teleoroentgenograms were made at least every six months, and electrocardiograms every three months. Since it is logical to assume that a valvular lesion has to exist for a considerable length of time before it will affect the size of the heart, it was necessary in each case to estimate how long the lesion had existed, and whether during the period of observation the rheumatic process had been quiescent. It is well known that even low-grade rheumatic activity sometimes produces slight degrees of cardiac dilatation which may later subside. Furthermore, the murmurs heard may be related to the tem-

porary dilatation and have no permanent significance. Children with clinical or laboratory signs of rheumatic activity were, therefore, excluded from this study.

It was also thought of interest to see whether any indication of enlargement of the left auricle could be found in these fifty-five children whose only auscultatory abnormality was an apical systolic murmur. The findings in this group of children were compared with those in eight children with characteristic, rumbling, apical diastolic murmurs, in addition to apical systolic murmurs, and with those in thirteen children with apical systolic murmurs and soft, short, apical diastolic murmurs of doubtful significance.

Control Group.—In order to familiarize ourselves with the normal variations, 101 healthy girls,* ranging in age from 7 to 15 years, were examined. The height and weight of each child were determined, and the type of body build was noted. Attempts to obtain histories were unsatisfactory because these children were separated from their parents and lived in an institution. The heart of each child was examined by two observers, and none showed clinical evidence of enlargement or abnormal auscultatory signs. The blood pressure of each child was measured and found to be within normal limits.

The methods used will be outlined as briefly as possible.

METHODS

Fluoroscopy

Every child was examined in the frontal, as well as in the left and right oblique, planes.

Anteroposterior Position.—In this position the lie of the heart, whether normal, vertical or transverse, was noted, and the cardiac silhouette was studied for any abnormalities of contour.

Left Anterior Oblique Position.—In this position the "angle of clearance,"† or degree of rotation necessary to separate the lower dorsal border of the heart from the vertebral column, was determined.‡ In making this determination the posture of the child was found to be extremely important. If the child swayed or rotated, the result was unreliable. Every determination was repeated several times with the central ray of the x-ray cone in the center of the fluoroscopic screen.

Right Anterior Oblique Position.—A rotation of 55 to 70 degrees was usually satisfactory for examining patients in this position. It was often found desirable to rotate the patient slightly during the course of the examination, since the optimal degree of rotation varied with each patient. In order to visualize the dorsal border of the heart clearly in this position, it was necessary to outline the esophagus with barium. A small amount of a fairly thick barium paste was put into the child's mouth and he was asked not to swallow until he was under observation.

Since in normal children the left auricle produces a slight curve which varies with body build, the significance of a slight displacement of the esophagus often remains doubtful. We regarded the left auricle as enlarged when there was a distinct hesitation in the descent of the barium as it reached the top of the auricular curve, with diversion of the stream to the left at this point. Furthermore, in the absence of aortic disease, the auricular curve was more prominent than the upper curve produced by the fused impression of the aorta and left bronchus. The left auricle was considered enlarged if the prominence of the second curve did not disappear completely with deep inspiration. It was found important not to overfill the esophagus with barium. Slight degrees of left auricular enlargement rarely

*The permission to examine these children was obtained through the cooperation of Dr. Luke Fleming and of the Sisters of Mercy, Tarrytown, New York. Teleoroentgenograms were not taken on children in the control group.

†Through the courtesy of Dr. May G. Wilson, a turntable similar to the one used by her was constructed for us at the New York Hospital. This turntable has been used routinely for examining patients in the left and right oblique positions.

caused compression of the esophagus. The curves seen with a greatly distended esophagus were in most instances found to be artifacts. The best results were obtained when the esophagus was outlined as a column about the thickness of a lead pencil.

Teleoroentgenograms

Routine teleoroentgenograms in the frontal and oblique planes were taken of all rheumatic children on admission, and approximately every 6 months thereafter.* Additional teleoroentgenograms were obtained if the child developed rheumatic activity.

Anteroposterior Position.—Since tracings of teleoroentgenograms were used for the measurement of frontal areas, it was important to visualize the apical region as well as possible. All exposures were therefore taken in the same respiratory phase, namely, moderately deep inspiration. Orthodiagraphy was not attempted because of the difficulty of making children sit still for a sufficient length of time.

Left Anterior Oblique Position.—It was thought of interest to see if the value for the angle of clearance, as determined by fluoroscopy, would agree with that obtained teleoroentgenographically. All teleoroentgenograms in this position were taken at a rotation of 55 degrees. Although it was difficult to take teleoroentgenograms at a specified rotation, fairly satisfactory results were obtained in most instances.

Right Anterior Oblique Position.—Teleoroentgenograms taken in this position were, in our opinion, less satisfactory than fluoroscopic examinations for showing slight backward displacement of the esophagus. Plates were therefore not taken routinely in this position.

RESULTS

Control Group

Angle of Clearance.—Of the 101 children, seventy-eight, or 77 per cent, had an angle of less than 55 degrees. In twenty-two children, or 21 per cent, the angle of clearance was equal to 55 degrees, and in 1 child was more than 55 degrees. The child whose angle of clearance was more than 55 degrees was examined on two occasions with the same results.

No definite correlation was found between the angle of clearance and the following factors: age, body build, height of the diaphragm, position of the heart, and state of nutrition. We agree, however, with Wilson's statement that typically vertical hearts tend to clear at smaller degrees of rotation than transverse hearts.

Among our controls, in contrast to Wilson's observations in 119 normal children, an angle of clearance of 55 degrees was found in one-fifth of the cases (21 per cent). In Wilson's control group the angle of clearance was less than 55 degrees in 97 per cent, and she therefore concluded that an angle of 55 degrees, or more, was abnormal, indicating enlargement of the left ventricle. In view of the high percentage of normal children whose hearts we were unable to clear at less than 55 degrees, our findings suggested that only angles of more than 55 degrees could be considered abnormal.

*At the suggestion of Dr. Hugo Roesler, of Philadelphia, exposures of 1 second were used to include both phases of the cardiac cycle and thus record the maximum size of the heart.

No history or evidence of heart disease was found in the child with an angle of clearance of more than 55 degrees. The examination of some children is unsatisfactory, and we think it probable that this child failed to stand properly. We have met with the same difficulty in our group of rheumatic children.

Esophagram.—No displacement of the esophagus was observed in any of these children.

Rheumatic Group

1. *Apical Systolic Murmurs, fifty-five children:* (a) *Children with constant apical systolic murmurs and cardiac enlargement, seven children.*—Of the fifty-five children with constant apical systolic murmurs, only seven showed cardiac enlargement on physical examination. The area of cardiac dullness extended beyond the midclavicular line, and, in the opinion of three different observers, cardiac enlargement was present. According to the criteria of the New York Heart Association,³ these seven children should be classified as cases of mitral insufficiency. The data in regard to the rheumatic history, duration of disease, period of quiescence, period of observation at Irvington House, angle of clearance, enlargement of the left auricle, enlargement on physical examination, and enlargement of the frontal area are presented in Table I. It will be seen that the duration of the disease in every case was three years, or more, and that none of the children had shown any signs of rheumatic activity for at least twenty-five months, as determined from the clinic and hospital records and the period of observation at Irvington House.

TABLE I
ANGLE OF CLEARANCE IN PATIENTS WITH MITRAL INSUFFICIENCY

NO. OF CASES	PATIENT	AGE (YR.)	SEX	NO. OF ATTACKS AND AGE AT EACH	QUIESCENCE (MO.)	DURATION OF DISEASE (YR.)	OBSERVATION (MO.)	ANGLE	L. A.	P. E.	AREA
1	3322 L.A.	12	F	7 Ch*	30	5	17	70°	—	+	+
2	3210 B.Z.	12	F	10 Ch 4 P	48	8	29	70°	—	+	+
3	3301 M.S.	10	M	8 P 7 P	35	3	12	70°	—	+	—
4	3329 A.R.	11	F	4 P and C 8 P and C	36	7	20	65°	—	+	—
5	3378 D.G.	13	F	5 Scarlet 5 Jt. P 11 C	25	8	8	65°	—	+	+
6	3287 J.M.	12	F	6 P 7 P 9 P	42	6	22	70°	—	+	—
7	3403 R.A.	9	F	5 P	48	4	6	70°	—	+	+

*The following abbreviations and symbols are used in all tables:

Ch.	Chorea	P.E.	Physical Examination
P.	Polyarthritis	L.A.	Left Auricle
C.	Carditis	H.D.	Heart disease discovered
Jt. P.	Joint pains	+	Enlarged
Angle.	Angle of Clearance (Wilson)	—	Within normal limits
M.	Male	Area.	Frontal Area
F.	Female		

TABLE II

ANGLE OF CLEARANCE IN PATIENTS WITH POTENTIAL HEART DISEASE

NO. OF CASES	PATIENT	AGE (YR.)	SEX	NO. OF ATTACKS AND AGE AT EACH	QUIESCENT (MO.)	DURATION OF DISEASE (YR.)	OBSERVATION (MO.)	ANGLE	L. A.	P. E.	AREA	REMARKS
1	3395 N.W.	11	M	9½ P	18	1½	6	55°	-	-	-	Poor pos- ture
2	3333 I.B.	12	M	8 P, C ?	52	4	13	55°	-	-	-	
3	3293 A.B.	12	M	9 P and C 10 Ch	28	3	15	55°	-	-	-	
4	3269 C.F.	10	M	7 Ch 7 P 7 P and C 8 Ch	22	3	20	55°	-	-	-	
5	3355 M.F.	10	M	7 P and C	42	3½	14	60°	-	-	+	
6	3316 I.K.	9	M	5 P 8 C	24	4	10	60°	-	-	-	
7	3234 P.M.	14	M	10 P 10 P 12 P and C	24	4	20	65°	-	-	-	
8	3184 H.O.	12	M	6 P and C	72	6	23	55°	-	-	-	
9	3335 R.R.	9	M	7 P and C 7 P and C	17	2	10	55°	-	-	+	
10	3330 R.A.	11	M	9 P and C	20	2	16	55°	-	-	-	
11	3348 E.C.	13	M	8 P 10 P 12 P	13	5	8	55°	-	-	-	
12	3375 C.C.	12	M	6 P and Ch 11 Ch	25	6	7	50°	-	-	-	
13	3205 H.D.	10	M	5 Jt. P 7 C	24	5	22	55°	-	-	-	
14	3374 D.E.	10	M	7 P and C	26	3	12	45°	-	-	-	
15	3237 D.O.	10	M	6 P and C	48	4	17	55°	-	-	-	
16	3385 J.O'N.	9	M	7 P and C	30	2	12	50°	-	-	-	
17	3350 H.P.	10	M	7 P and C 8 P and C	18	3	14	55°	-	-	-	
18	3297 D.R.	11	M	9 P and C	24	2	18	55°	-	-	-	
19	3299 A.R.	9	M	4 P and C?	48	5	12	55°	-	-	-	
20	3369 S.R.	13	M	4 Scarlet 4 C	108	9	10	50°	-	-	-	
21	3371 D.S.	13	M	8 P 11 P and C	22	5	10	50°	-	-	-	
22	3356 F.S.	13	M	9 P and C 12 P	18	4	14	55°	-	-	-	
23	3337 A.S.	15	M	12 P	36	3	9	55°	-	-	-	
24	3377 A.B.	9	F	6 P and C	30	3	12	50°	-	-	-	
25	3261 D.B.	13	F	11 C, P and Ch	22	2	18	55°	-	-	-	

2

The angle of clearance was uniformly increased to a value well above 55 degrees, and no enlargement of the left auricle could be demonstrated in any instance. Enlargement of the frontal area was present in only four of these seven cases.

(b) *Children with constant apical systolic murmurs but without cardiac enlargement on physical examination, forty-eight children.*—All of these children had clear-cut rheumatic histories; in only seven cases, Nos. 39, 40, 41, 42, 43, 44, and 45, was there a history of "pure" chorea. In no instance was cardiac enlargement demonstrable on physical examination. According to the criteria of the New York Heart Association, these children would be classified as cases of potential heart disease. The data in regard to rheumatic history, period of quiescence, duration of disease, period of observation at Irvington House, angle of clearance, enlargement of the left auricle, and enlargement of the frontal area are presented in Table II. The average duration of disease in this group of children with potential heart disease was four years, with a minimum of two years. The period of quiescence was thirteen months or longer.

The angle of clearance showed the following values:

1 child	45 degrees
10 children	50 degrees
26 children	55 degrees
4 children	60 degrees
7 children	65 degrees

Thirty-seven, or 77 per cent, of these children with potential heart disease showed an angle of clearance of 55 degrees or more. If we accept Wilson's conclusion that an angle of 55 degrees, or more, indicates a definite abnormality, the percentage of children in this group with an enlarged angle of clearance is almost identical with that found by Wilson in a similar group of sixty-four children with potential heart disease. In our own control group of 101 children, however, angles of clearance of 55 degrees were obtained in twenty-two children (21 per cent), suggesting that a value of 55 degrees was within the limits of normal. Therefore, only values of 60 degrees, or more, have been considered abnormal.

In analyzing the results summarized in Table II, the difficulties inherent in the method must be taken into consideration. In some children with poor posture or slight scoliosis of the thoracic vertebrae, with displacement of the heart to the left, enlarged angles of clearance were obtained on repeated examinations, although the diameter and contour of the cardiac silhouette in the left anterior oblique position appeared to be entirely normal. Occasionally, marked development of the breasts interfered with a satisfactory examination. Cases No. 7, 39, 43, and 44 illustrate these difficulties.

In cases No. 5, 6, and 38, in which the angle of clearance was 60 degrees, and in cases No. 45, 46, 47, and 48, in which the angle of clearance was 65 degrees, the curve of the left lower cardiac border in the left

oblique position seemed accentuated. It was thought probable, therefore, that the left ventricle was slightly enlarged in these seven cases, although no enlargement was demonstrable on physical examination and the frontal area was increased in only two instances (cases No. 5 and 47).

2. *Apical Systolic and Apical Diastolic Murmurs, eight children.*—In children, well-marked, rumbling, diastolic or presystolic crescendo murmurs, in the absence of aortic regurgitation, are generally accepted as an indication of mitral stenosis. This type of murmur is rarely heard in children less than 10 years of age.

According to the criteria of the New York Heart Association,⁶ the roentgenologic finding most characteristic of mitral stenosis is enlargement of the left auricle. It was thought of interest to see in how many instances left auricular enlargement was demonstrable in children with typical apical diastolic murmurs. At the same time, the findings in regard to the angle of clearance, enlargement on physical examination, and enlargement of the frontal silhouette were noted. Only eight children with murmurs considered by several observers to be characteristic of well-established mitral stenosis were included in this group. The data are presented in Table III. The duration of the disease in these eight children was four to six years, and the period of quiescence was twenty-one months, or longer.

TABLE III

ANGLE OF CLEARANCE AND SIZE OF THE LEFT AURICLE IN PATIENTS WITH MITRAL INSUFFICIENCY AND MITRAL STENOSIS

NO. OF CASES	PATIENT	AGE (YR.)	SEX	NO. OF ATTACKS AND AGE AT EACH	QUIESCENT (MO.)	DURATION OF DISEASE (YR.)	OBSERVATION (MO.)	ANGLE	L. A.	P. E.	AREA	REMARKS
1	3313 F. C.	16	M	10-12 Jt. P 11 C, nodules	45	6	10½	50°	+	-	-	Apical diastolic thrill
2	3366 M. D.	12	F	6 Ch 10 P	30	6	14	70°	+	+	+	
3	3091 M. H.	13	F	8 C 11 C	24	5	32	65°	+	+	+	
4	3224 J. M.	13	M	9 H. D. 11 C	21	4	21	55°	-	-	-	
5	3282 P. N.	14	F	9 Ch 11 Ch 12 P	31	5	16½	60°	-	-	-	
6	3110 R. S.	10	F	5 Jt. P 7 H. D. 7½ C	24	4	31	70°	+	+	-	Apical diastolic thrill
7	3150 D. W.	12	F	5-7 Jt. P	60	5	27	65°	-	-	-	Apical diastolic thrill
8	3292 L. DeR.	15	F	10 Ch	60	5	19	55°	+	-	-	

In this group of eight children with mitral insufficiency and stenosis, the angle of clearance was increased in five instances. In two of these five cases, cardiac enlargement was also demonstrable on physical examination and by measurements of the frontal area. In one case enlargement was present on physical examination but the frontal area was normal. In two cases the angle of clearance was increased without demonstrable cardiac enlargement on physical examination or by measurements of the frontal plane of the teleoroentgenogram. Only five of these eight children showed enlargement of the left auricle. In only one instance (case No. 2) was the enlargement of the left auricle sufficiently marked to displace the esophagus in the anteroposterior position as well as in the right anterior oblique position. In no instance did the left auricle extend to the left bronchus in the left anterior oblique position and obliterate the "tracheal window."

3. *Apical Systolic, and Short, Soft Apical Diastolic, Murmurs of Doubtful Significance, thirteen children.*—Every pediatrician and cardiologist who has rheumatic children under his care is aware that a short, soft, atypical diastolic murmur is sometimes heard at the apex. Often this murmur is only audible after exercise. The bruit under discussion sounds like a murmur and usually is not considered to be a third heart sound. The interpretation of this type of murmur is extremely difficult. It may indicate a progressive lesion, in which case it gradually becomes a typical diastolic rumble. It may persist for several years without becoming more marked, or it may disappear completely. Most observers are of the opinion that with this type of murmur the diagnosis of mitral stenosis is unwarranted. The term "potential mitral stenosis" has been suggested for these cases by Schlesinger.⁷

The data in regard to the angle of clearance, enlargement of the left auricle, enlargement on physical examination, and enlargement of the frontal silhouette in thirteen children who, in the absence of rheumatic activity, have shown this type of diastolic murmur for a considerable period of time are presented in Table IV. The minimum duration of the disease in this group was two years, and the period of quiescence, twelve months, or more.

In eleven of the thirteen children with atypical apical diastolic murmurs the angle of clearance was increased. In four of these eleven cases, cardiac enlargement was also demonstrable on physical examination and by measurements of the frontal area. In two of the eleven cases cardiac enlargement was apparent on physical examination but not by measurements of the frontal plane. In one case the frontal area was increased above normal, although no enlargement was present on physical examination. In four cases the angle of clearance was increased without demonstrable enlargement on physical examination or by measurements of the frontal plane. The left auricle was enlarged in six of these thirteen children. In only one instance (case No. 12) was the enlargement of the left

auricle sufficiently marked to displace the esophagus in the anteroposterior position. In no instance did the left auricle extend to the left bronchus in the left anterior oblique position and obliterate the "tracheal window."

DISCUSSION

In the material presented above an attempt has been made to see how often enlargement of the left ventricle could be detected by the method

TABLE IV

ANGLE OF CLEARANCE AND SIZE OF THE LEFT AURICLE IN PATIENTS WITH APICAL SYSTOLIC, AND SHORT, SOFT APICAL DIASTOLIC, MURMURS OF DOUBTFUL SIGNIFICANCE

NO. OF CASES	PATIENT	AGE (YR.)	SEX	NO. OF ATTACKS AND AGE AT EACH	QUIES. CENT (MO.)	DURATION OF DISEASE (YR.)	OBSERVATION (MO.)	ANGLE	L. A.	P. E.	AREA
1	3252 T. C.	11	M	9 C	34	3	18	70°	+	+	+
2	3323 J. C.	10	F	8 P	24	2	10	65°	-	+	-
3	3262 T. D.	9	F	6 C 7 C 8 C	12	3	18	65°	-	+	-
4	3190 E. DeL.	15	F	5 P	116	10	22	60°	+	-	+
5	3243 T. G.	10	F	6 P 9 C	14	4	18	55°	-	-	-
6	3329 O. K.	10	F	5 Ch 6 Ch 7 Ch	29	5	16	65°	-	+	+
7	3290 G. L.	13	F	8 Ch 12 Ch and C?	13	5	13	55°	-	-	-
8	3247 M. M.	9	F	6 Ch 6 C and Ch 7 C and Jt. P	24	3	18	60°	-	-	-
9	3225 A. P.	11	M	9 P	24	2	21	60°	+	-	-
10	3448 R. R.	12	M	7 P 8 C 9 P 10 C	14	5	15	60°	+	-	-
11	3309 F. S.	9	F	7 C	24	2	11	65°	-	+	+
12	3372 A. T.	9	M	4 P 6 P 7 P	30	5	14	65°	+	+	+
13	3332 V. D.	8	M	6 P	28	2	11	60°	+	-	-

described by Wilson¹ in two groups of rheumatic children whose only auscultatory abnormality was an apical systolic murmur. The first group consisted of seven children with mitral insufficiency (children with apical systolic murmurs and definite enlargement on physical examination). The second group consisted of forty-eight children with potential heart disease (children with rheumatic histories and constant apical systolic murmurs without demonstrable cardiac enlargement on physical examination).

According to Wilson's findings, an "angle of clearance" of 55 degrees, or more, was abnormal, indicating left ventricular enlargement. In a control group of 101 normal girls examined by us, however, an angle of clearance of 55 degrees was found in twenty-two children, or 21 per cent. We, therefore, concluded that only values above 55 degrees could be considered abnormal.

In the seven children with mitral insufficiency, the angle of clearance was definitely increased in every instance. However, in spite of the presence of enlargement on physical examination and the increased angle of clearance, enlargement of the frontal areas was noted in only four of these seven cases.

In forty-eight children with potential heart disease, the angle of clearance was found to be above 55 degrees in eleven cases. In four of these eleven cases, however, the determinations were unsatisfactory for reasons already discussed. In the seven cases in which it was thought that the increased angle of clearance might represent enlargement of the left ventricle, a value of 60 degrees was obtained in three cases and a value of 65 degrees in four. The frontal areas were normal in five of these seven children.

In view of the many factors involved and the difficulties of making the determinations in children, too much weight cannot be placed on small numerical differences. Hearts that seemed enlarged on physical examination usually showed angles of clearance well above 55 degrees (65 or 70 degrees). It was difficult to be sure that an angle of clearance of 60 degrees represented a definite abnormality in cases in which the heart seemed normal on physical examination and in teleoroentgenograms taken in the anteroposterior and left oblique positions. The measurement of the angle of clearance, in our opinion, is a valuable procedure, not because it is possible to draw a sharp line between what is normal and what is abnormal, but because it so often corrects an erroneous impression of left ventricular enlargement. In patients with high diaphragms and transverse hearts, the appearance of the heart in the anteroposterior position often suggests left ventricular enlargement. In this type of patient, if the angle of clearance is 55 degrees or less, we believe that it is safe to conclude that the heart is not enlarged. Furthermore, although the significance of a slight increase in the angle of clearance is often difficult to interpret, fluoroscopic examination with a turntable at known degrees of rotation is of value. With this method, examinations in the left anterior oblique position tend to be more uniform, and variations in different patients and changes in the same patient at different times can be detected more readily.

It is of interest that, in the group of fifty-five children who had an apical systolic murmur, enlargement of the left auricle could not be

demonstrated in a single instance. On the other hand, even in cases of clear-cut mitral insufficiency and stenosis of several years' duration, this chamber was not uniformly enlarged.

The findings in eight children with typical mitral insufficiency and stenosis and in thirteen children with apical systolic murmurs and short, soft, diastolic murmurs of doubtful significance have been compared with those in seven children with mitral insufficiency and in forty-eight children with potential heart disease.

The angle of clearance was increased in sixteen of these twenty-one children. In addition to an increased angle of clearance, enlargement on physical examination or by measurement of the frontal plane was present in ten of these sixteen cases.

It has been emphasized by Nemet⁸ and Roesler⁹ that measurements of the frontal area are of little value in borderline cases of cardiac enlargement. The range of variations in the size of the normal heart is so great that the results of such measurements are unreliable except in hearts that are obviously enlarged or obviously normal. A small heart may enlarge considerably before it exceeds the upper limit of normal, whereas a heart which is already near the normal limit in size would have to enlarge only slightly to be considered abnormal.

On the other hand, in view of the fact that the left ventricle forms so large a part of the heart, it seemed possible that an increase in the size of this chamber, suggested by an enlarged angle of clearance, might be confirmed by finding an enlarged frontal area.

In the whole group of seventy-six rheumatic children, an enlarged angle of clearance was found in thirty. The frontal area, however, was found to be increased in only thirteen of these thirty children, or in 43 per cent.

It was thought that the presence or absence of an enlarged left auricle would help us to come to some conclusion as to the correct anatomic diagnosis in children with atypical apical diastolic murmurs. In view of the variable findings in children with definite mitral stenosis of several years' standing, it is impossible to attach much significance to the absence of enlargement of the left auricle. In children in whom the apical diastolic murmur is not characteristic, the presence of an enlarged left auricle is suggestive evidence that mitral stenosis is developing, but a normal left auricle does not rule out this possibility. In our opinion, it is only by following the same children over a period of years that the significance of a slight displacement of the esophagus in the right anterior oblique position can be interpreted correctly.

Since so much emphasis is placed on the presence or absence of enlargement in making anatomic diagnoses in rheumatic heart disease, it is important to bear in mind the factors that cause cardiac enlargement. The valvular defect is rarely sufficiently marked to produce dilatation or hypertrophy by itself. Enlargement is usually the result of the combina-

tion of an inefficient, diseased myocardium and a slight or moderate valvular lesion. According to Lewis¹⁰ and Palmer,¹¹ with a given amount of myocardial damage the heart will not enlarge further. It is only when the lesion is progressive that progressive enlargement takes place. It is well known that a small number of patients with clear-cut mitral stenosis or aortic insufficiency of several years' standing fail to develop demonstrable enlargement. In these cases the myocardium has probably made a good recovery and is able to compensate for the valvular defect. Persistent but nonprogressive cardiac enlargement in children with no detectable evidence of rheumatic activity may indicate a chronically damaged myocardium, rather than a marked valvular defect. From the point of view of prognosis, the most important thing to ascertain is whether the size of the heart is increasing, decreasing, or remaining stationary. If the child is not growing too fast, changes in the size or contour of the heart can best be detected by the method used by Palmer,¹¹ namely, the superposition of outlines obtained by making tracings of comparable teleoroentgenograms or orthodiagrams.

CONCLUSIONS

1. In cases of questionable cardiac enlargement it is usually impossible to be certain of a definite abnormality on the basis of a single radiologic measurement.

2. The chief value of any radiologic procedure in cases of early rheumatic heart disease is to detect changes in the size or contour of the heart in the same patient at different times.

3. The measurement of the "angle of clearance" (Wilson), by means of a turntable, is of value because it tends to standardize the fluoroscopic examination of the patients in the left oblique position and makes the findings in the same patient at different times comparable. Furthermore, this procedure is an aid in ruling out left ventricular enlargement in patients with high diaphragms and transverse hearts, in whom the heart appears enlarged to the left in the anteroposterior position.

4. Early enlargement of the left auricle can best be demonstrated by the backward displacement of the barium-filled esophagus. The presence of an enlarged left auricle suggests that mitral stenosis may be developing, but the absence of enlargement of this chamber does not exclude this possibility.

5. In accordance with the observations of previous investigators, we found that measurements of the frontal area proved of little value in establishing a definite abnormality in cases of early rheumatic heart disease in children.

REFERENCES

1. Wilson, May G.: Clinical Radioscopic Studies of the Heart in Children, *Am. J. Dis. Child.* 47: 750, 1934.
2. Evans, William: The Course of the Oesophagus in Health and in Disease of the Heart and Great Vessels, Privy Council, Medical Research Council, London, 1936.

3. Danzer, C. A.: The Cardio-Thoracic Ratio. An Index of Cardiac Enlargement, *Am. J. M. Sc.* 157: 513, 1919.
 4. Hodges, P. C., Adams, W., and Gordon, W.: Estimation of Cardiac Area in Children, *J. A. M. A.* 101: 914, 1933.
 5. Kurtz, C. M.: *Orthodiasecopy*, New York, 1937, The Macmillan Co.
 6. Criteria for the Diagnosis and Classification of Heart Disease, 1932, New York Heart Association.
 7. Schlesinger, B.: The Public Health Aspect of Heart Disease in Childhood, *Lancet* 1: 593, 1938.
 8. Nemet, G.: Guide to Radiologic Diagnosis in Heart Disease, Heart Committee of the New York Tuberculosis and Health Association, Inc., 1932.
 9. Roesler, Hugo: *Clinical Roentgenology of the Cardiovascular System*, Springfield, Ill., 1937, Charles C. Thomas, Publisher.
 10. Lewis, T.: *Diseases of the Heart*, New York, 1936, The Macmillan Co.
 11. Palmer, J. A.: *The Development of Cardiac Enlargement in Disease of the Heart: A Radiological Study*, Privy Council, Medical Research Council, London, 1937.
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Corrigendum

In the article, "The Effects of Alkalosis and of Acidosis Upon the Human Electrocardiogram," by Paul S. Barker, M.D., E. Lee Shrader, M.D., and Ethel Ronzoni, Ph.D., which appeared in the February, 1939, issue of the *Journal*, the phrase "hydrogen ion concentration," wherever it appears, should be read "pH."

MEASUREMENT OF CIRCULATION TIME WITH CALCIUM GLUCONATE IN PATIENTS RECEIVING DIGITALIS. WITH ELECTROCARDIOGRAPHIC STUDIES

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A SIMPLE, harmless method for determining the circulation time is useful in the diagnosis of cardiac diseases. Recently, calcium gluconate was proposed to fulfill such requirements. When so used, it must be injected rapidly into the veins of patients many of whom are taking digitalis, and among these are some with definitely diseased hearts. Thus, the possibility of the synergistic action of calcium and digitalis arises. Consequently, one must violate certain safety precautions, to which the medical profession's attention has been called.

Numerous investigators^{1-4, 9, 21} have shown that calcium and digitalis have an additive or synergistic effect on the heart, and that calcium, when injected rapidly, is a potentially dangerous drug. Much of this experimental work was done on animals under circumstances not comparable to those existing when calcium is used in measuring circulation times in man. Golden and Brams³ used dogs weighing 8 to 12.5 kg. and gave 50 to 90 per cent of the calculated lethal dose of digitalis intravenously in single doses. These large doses produced a rise in blood pressure, heart block, and ventricular tachycardia. Obviously, digitalization is never intentionally carried this far in human subjects. These workers then injected 15 to 17.5 c.c. of a 20 per cent calcium gluconate solution into the vein at a rate of 4 c.c. per minute. This resulted in ventricular tachycardia, ventricular fibrillation, and, finally, death. These results led them to advise against the use of calcium intravenously in any patient who is receiving digitalis.

On the other hand, Goldberg⁵ has injected 2.5 c.c. of a 20 per cent calcium gluconate solution rapidly into the vein (1 to 2 sec.) in 500 patients, many of whom had heart disease and were digitalized, without noting any harmful effects. Likewise, Baer and Slipakoff⁶ used the same technique on 356 similar patients with no untoward reactions. Berliner⁷ found that 10 c.c. of a 20 per cent calcium gluconate solution had to be injected rapidly, i.e., within 15 seconds, to produce electrocardiographic changes, namely, bradycardia and flattening or inversion of P and T waves. These changes were transient. In two cases there was brief sinus arrest; this occurred in frail individuals.

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Received for publication Feb. 15, 1932.

Because of the previous warnings we decided to investigate further the use of calcium for measuring circulation time, and to note any changes that occur in the electrocardiogram during its administration. For comparison, the circulation time was measured with decholin.

PROCEDURE

Each patient was placed in a recumbent position for 20 to 30 minutes before the tests were begun. With the arm at the level of the right auricle (5 cm. below the plane of the manubriosternal junction), the solution was injected through an 18-gauge needle into an antecubital vein as rapidly as possible. This took about 1 second. It was found that the readings checked when the same amount of time was consumed for each injection. The circulation time was determined with a stop watch from the beginning of the injection to the first moment the sensation of bitterness or heat was felt in the tongue. At least 1 minute was allowed to elapse after the tourniquet was released before the solutions were injected. We used 5 c.c. of a 20 per cent decholin solution followed by 2.5 to 3 c.c. of a 20 per cent calcium gluconate solution, and three minutes later 3.5 to 5 c.c. of a 20 per cent calcium gluconate solution. All of these were injected through the same needle. Sometimes the calcium was injected before the decholin, but the order seemed to make no difference in the results.

When electrocardiographic studies were made, the three standard leads were taken first. Lead II was then taken again, and, with the patient remaining in the circuit, 2.5 to 5 c.c. of a 20 per cent calcium gluconate solution were injected as described above. The circulation time was confirmed by standardizing the tracing at the beginning of the injection and at the first sensation of heat in the tongue. The tracing was continued for at least 2 minutes, and another strip taken in 4 to 5 minutes.

RESULTS

Patients were arbitrarily divided into two classes: those with a decholin circulation time of less than 20 seconds, and those with a circulation time of more than 20 seconds. The results are shown in Tables I and II. It will be seen that Table I comprises patients without cardiac disease and patients whose hearts were in a good state of compensation. Table II includes patients with signs and symptoms of congestive heart failure or other conditions that yield prolonged circulation times, such as myxedema or polycythemia. We found that all patients with congestive heart failure had circulation times in excess of 20 seconds; however, not all patients whose circulation times were longer than 20 seconds necessarily had congestive heart failure. It was interesting to note that one patient (Case 49, Table II) with auricular flutter and congenital heart disease showed a circulation time of 22.4 seconds (decholin) when he had no heart failure, as judged by clinical observations. In this case it was technically impossible to use the antecubital veins, so recourse had to be made to the wrist veins. This may possibly account for the delay, although it is more probable that the figures represent a true slowing of the circulation. It was found that when the decholin time was below 20 seconds, 2.5 to 3 c.c. of calcium gluconate solution yielded results that corresponded closely with 5 c.c.

TABLE I
PATIENTS WITHOUT CARDIAC DISEASE OR PATIENTS WHO HAD NO HEART FAILURE

DIAGNOSIS	DECHOLIN			CALC. GLUC.		
	AMT. (C.C.)	TIME (IN SECONDS)	AMT. (C.C.)	TIME (IN SECONDS)	AMT. (C.C.)	TIME (IN SECONDS)
1. (4-1 distress	5	15.6	2.5	19.2	2.6	18
2. Possible thyrotoxicosis	5	12.5	2.5	12.0		
3. Tachycardia	5	9.2	2.5	10.4		
4. Obesity	5	16.0	5 (10%)	14.3		
5. Obesity	5	15.4	5 (10%)	16.7		
1 week later	5	13.4	3	17.0		
6. Obesity	5	17.0	3	18.0	4.0	15.4
1 week later	4	18.5	3	15.0	4.0	17.5
7. Obesity	5	12.2	3	12.4	5.0	14.5
*8. Obesity	5	11.4	3	13.6		
2 weeks later, off digitalis	5	11.8	3	13.6	4.0	13.0
9. Obesity	5	12.7	3	17.0		
1 week later	5	11.6	3	11.2	5.0	10.2
10. Pneumothorax	5	10.0	5 (10%)	9.8		
11. Malnutrition	5	13.4	3	15.1		
12. Arteriosclerosis	5	12.2	3	14.6		
13. Obesity, anemia	5	10.0	3	10.0	5.0	9.8
14. Thyrotoxicosis, B.M.R. + 42%	3	11.2	2.5	12.4		
1 week later B.M.R. + 20%			3.0	12.2		

*Patient was taking digitalis

TABLE I—CONT'D

15. Thyrotoxicosis	5	8.9	2.0	8.2	
16. Thyrotoxicosis	3	9.8	2.5	10.0	
17. Thyrotoxicosis	3	7.4	3.0	7.1	
18. Thyrotoxicosis 4 days later	5	9.4	3.0	8.6	
19. Thyrotoxicosis	5	8.2	2.5	10.3	3.0
20. Thyroid heart disease, anemia, ascites	5	13.4	3.0	7.4	10.1
21. Chr. nephritis, hypertension	5	12.5	3.0	14.0	
22. Rheumatic heart disease, anemia	5	13.0	2.6	12.4	4.0
23. Hypertension	5	15.7	5 (10%)	14.3	
1 week bed rest	5	13.6	3	15.6	
24. Hypertension	5	18.0	3	11.8	
2 weeks bed rest	5	15.8	2.0	24.0	3.0
25. Rheumatic heart disease, mildly active	5	12.2	5 (10%)	15.7	19.0
26. Rheumatic heart disease	5	15.4	3	13.4	
*27. Hypertension	5	14.0	2.5	16.4	
*28. Paroxysmal auricular fibrillation	5	8.4	2.6	15.5	3.5
29. Rheumatic heart disease, marked anemia	5	10.4	2.5	10.4	4.0
30. Polycythemia, under treatment	5	11.6	3.0	10.4	4.0
31. Myxedema, tetany	5		3.0	11.2	5.0
2 days later			5 (10%)	20.4	10.2
50. Acute bacterial endocarditis, following pneumonia	5	19.0	3.0	23.6	5 (10%)
	5	12.0	3.0	14.5	3.0
					25.41
					12.5

*This calcium injection followed previous one by 2½ minutes. 1 c.c. calcium gluconate solution 3 minutes later gave 19.2 sec.

TABLE II
PATIENTS WITH CARDIAC DISEASE OR OTHER CONDITIONS RESULTING IN PROLONGED CIRCULATION TIMES

DIAGNOSIS	DECHOLIN				CALC. GLUC.			
	AMT. (C.C.)	TIME (IN SECONDS)	AMT. (C.C.)	TIME (IN SECONDS)	AMT. (C.C.)	TIME (IN SECONDS)	AMT. (C.C.)	TIME (IN SECONDS)
32. Nephritis, hypertension	5	20.0	5.0	18.0				
33. Auricular fibrillation, compensated	5	20.6	2.5	25.0	3	26.01		
34. Cor pulmonale, polycythemia	5	20.5	3.0	25.0	5	19.9		
35. Polycythemia	5	22.0	2.5	27.2	4	24.0		
*36. Auricular fibrillation, compensated	5	22.4	3.0	22.0	5	19.5		
37. Constrictive pericarditis	5	23.5	5.0	22.0				
After paracentesis (abdomen)	5	22.2	3.0	24.0	5	22.2		
After pericardial resection	5	18.2	3.0	24.0				
*38. Hypertension, left-sided heart failure	5	23.2	5.0	27.2				
*39. Chr. cor pulmonale, right-sided heart failure	5	25.0	2.5	42.0				
*40. Rheumatic heart disease, decompensated	5	28.4	3.0	38.6	5	24.6		
41. Myxedema	5	29.3	3.5	31.5				
Under treatment	5	32.2	3.0	55.0				
3 months later	5	20.0	3.0	22.0	5	20.0		
*42. Rheumatic heart disease, auricular fibrillation	5	17.0	3.0	13.0	5	15.6		
No change clinically	5	31.4	4.5	48.7				
*43. Hypertension, aneurysm of left vent.	5	31.6	3.0	43.4	5	36.0		
*44. Rheumatic heart disease, auricular fibrillation	5	36.4	5.0	40.6				
*45. Rheumatic heart disease, auricular fibrillation	5	37.0	5.0	61.5				
*46. Rheumatic heart disease, auricular fibrillation	5	45.0	2.6	--	2.6	--		
*47. Rheumatic heart disease, auricular fibrillation	5	49.2	2.5	--				
*Digitalis intoxication	5	44.6	2.5	--	3.5	57.6		
*2 days later	5	29.6	4.0	38.6				
*48. Aortic regurg., syphilis	5	27.6	3.0	--	4	48.0		
*49. Auricular flutter, congenital heart disease?	5	55.2	2.8	--	5.0	61.0		
*Patient taking digitals	5	22.4	3.0	27.7				

*Patient taking digitals

†Injection about 1 minute after previous calcium injection; third calcium injection of 4 c.c. gave 35.0 seconds, also with 1 minute interval

‡Solutions injected into wrist veins

of decholin in most of the cases. We finally settled on 3 c.c. of calcium gluconate solution because measurements with this amount checked better. However, when the decholin time became more prolonged the calcium time usually lagged far behind. In many cases there was no end point. Hence, we attempted to secure an end point by using larger amounts of calcium gluconate solution, up to 5 c.c. In a typical instance (Case 47, Table II), a patient with rheumatic heart disease and auricular fibrillation, severely decompensated, at first had a decholin time of 44.6 seconds; 2.5 c.c. of calcium gluconate solution gave no response, whereas 3.5 c.c. required 57.6 seconds. After digitalization to the point of toxicity (nausea, vomiting, pulsus bigeminus), the decholin time was reduced to 29.6 seconds, while 4 c.c. of calcium gluconate solution gave a circulation time of 38.6 seconds. A few days later, when all signs of toxicity had disappeared and the patient was much improved clinically, the decholin time became further reduced to 27.6 seconds; 3 c.c. of calcium gluconate solution still gave no response, and 4 c.c. gave an arm-to-tongue time of 48 seconds. In this case the decholin gave circulation times that paralleled the clinical improvement, whereas the calcium times were discordant.

Fifteen patients had been given full doses of digitalis prior to the use of calcium gluconate for measuring the circulation time. In no instance did we observe the slightest reaction from the rapid intravenous injections of calcium gluconate.

Electrocardiograms were made on eleven patients during the intravenous injection of calcium gluconate. Usually there was an initial increase of the heart rate (about 10 beats per minute) during the injection, followed by a gradual slowing that reached its maximum about 60 to 80 seconds after the start of the injection. In eight cases the rate returned to the basal level, and in three it fell 5 to 15 beats below the basal level. One patient, without cardiac disease, was given 2.5 c.c. of calcium gluconate solution. The electrocardiogram showed flattening of the P waves, and the T waves, which were previously low and diphase in Lead II, became inverted. Both returned to their previous state in 2 minutes. Another patient (Case 47, Table II), with digitalis intoxication, referred to above, was given 4 c.c. of calcium gluconate solution and showed only a fall in pulse rate from 95 to 80. This patient's electrocardiogram showed depressed S-T segments and ventricular premature beats coupled with normal cycles. In no electrocardiogram were there changes in the QRS and Q-T intervals. No other noteworthy electrocardiographic changes occurred. On two occasions 5 c.c. of calcium gluconate solution were given to a patient (Case 38, Table II) with hypertensive arteriosclerotic heart disease who had been on full doses of digitalis and had been known to have a gallop rhythm for at least one year. He had no reaction nor did his electrocardiogram show any changes during the injection.

COMMENTS

It is difficult to reconcile the apparent harmlessness of calcium gluconate when it is used for measuring circulation time with the potential danger as evidenced by the clinical and experimental observations of Bowers and Mengle,¹ Lloyd,² Golden and Brams,³ and others.^{9, 21} However, it may be well to point out that Golden and Brams used 15 to 17.5 c.c. of 20 per cent calcium gluconate solution in dogs weighing 8 to 12.5 kg., or about 1.2 to 2.2 c.c. of 20 per cent calcium gluconate solution per kg. of body weight, as compared to 2.5 to 5 c.c. in human subjects weighing 60 to 80 kg., which is about 0.035 to 0.07 c.c. per kg., or one-thirtieth as much. The circulating blood volume is roughly proportional to the body weight. Hence both the digitalis and calcium concentrations in their dogs were far in excess of any ever obtained in man when calcium in small amounts is used for measuring circulation time. The two fatalities reported by Bowers and Mengle occurred in cases in which digitalis was being administered when calcium was injected, but the patients showed no evidence of congestive heart failure. In both cases a surgical operation had recently been performed, and the cause of the tachycardia was probably extracardiac. One patient received 10 c.c. of 10 per cent calcium gluconate solution, and the other 10 c.c. of 10 per cent calcium chloride solution. It is difficult to explain the cause of these deaths; however, their experimental evidence indicting calcium and digitalis is unconvincing because the dose of digitalis injected was in itself lethal in one dog, and approached lethal proportions in the other dogs. Lloyd used 10 per cent calcium chloride solution in his experiment on himself. Wolfe and Bellet⁹ reported a death following the use of 10 c.c. of 10 per cent calcium chloride solution in a 68-year-old person with advanced arteriosclerotic heart disease, heavily digitalized and almost in extremis before the injection of calcium. Bernstein and Simkins²¹ report two deaths attributable to calcium injections in digitalized patients. One apparently received 2.5 c.c. of 20 per cent calcium gluconate solution for measurement of circulation time, and died within a few hours. The other had recently had a cholecystectomy; he died suddenly during a calcium injection. Unfortunately, the details of these two deaths are not given. In the second case it is not certain whether the gluconate or the chloride salt of calcium was used, and the speed and quantity of the injection are also unknown. Thus another fact that may have bearing on the question is that calcium chloride was the drug used in three of the cases in which the patient died or serious cardiac consequences occurred. It may be well to point out a few differences between calcium chloride and calcium gluconate, besides the well-known difference in producing tissue irritation. Gram for gram, the chloride contains about three times as much calcium as the gluconate, and, furthermore, there is much greater ionization of the chloride than the

gluconate. Thus if one intends to use a calcium salt for measuring circulation time one should refrain from using the chloride.

Walters and Bowler¹⁰ showed that calcium is eliminated rapidly from the blood, and that there is no tendency for it to accumulate. They noted further, in two instances following rapid injections, that the calcium content of the heartblood taken immediately after death was twice that of the blood taken from the external jugular vein, and they concluded that the rapidity with which the injection is given, producing a sudden concentration of calcium in the blood, seems to be a factor in the relative toxicity of any dose. McGuigan and Higgins⁴ also showed that the toxic dose of calcium salts varies with the rate of injection, and that there is no specific danger in slow administration of calcium after digitalis, other than an additive effect. In one of their experiments on an 8 kg. dog, the rapid injection of 25 c.c. of 10 per cent calcium gluconate solution after 50 per cent of the fatal dose of digitalis killed the animal almost immediately, whereas in another dog the slow injection of the same amount of calcium after the same dose of digitalis was innocuous. These experiments suggest that it is a sudden increase in calcium ion concentration in the heart that is primarily responsible for the sudden deaths, rather than the synergism of calcium and digitalis.

In patients with congestive heart failure there is an increased circulating blood volume, together with a slowed circulation rate. Curiously enough, both factors serve to dilute the calcium before it reaches the heart, and consequently act as a safety mechanism.

Our results do not prove that calcium salts can be injected rapidly into patients, either digitalized or nondigitalized, without danger. However, the fact that we noted no ill effects from the use of calcium gluconate as a circulation time agent was undoubtedly a result of the small amount injected, so that the increase in the calcium content of the blood was so small by the time it reached the heart that it had no toxic effect; and in digitalized patients, who are known to be liable to the additive effects of calcium and digitalis, the heart was further protected by the diluting effects of congestive heart failure.

SUMMARY AND CONCLUSIONS

1. A comparison of decholin and calcium gluconate as agents in measuring circulation time reveals that 3 c.c. of 20 per cent calcium gluconate solution yield results that correspond closely with those obtained by 5 c.c. of decholin in patients with circulation times of less than 20 seconds.
2. In cases in which the decholin circulation time is prolonged beyond 20 seconds, the calcium time lags far behind, and calcium gluconate may give a blank reading in patients with extremely slow circulation time.
3. In fifteen patients who were receiving full doses of digitalis, calcium gluconate was used twenty-seven times without any clinical evidence of the slightest untoward effect.

4. In eleven patients, two of whom were receiving full doses of digitalis, electrocardiograms made during the administration of 2.5 to 5 c.c. of 20 per cent calcium gluconate solution showed no significant changes.

I wish to express my appreciation to Dr. Robert W. Keeton, Head of the Department of Medicine, for suggestions and advice in completing this work.

The 20 per cent calcium gluconate used in this study was made available through the courtesy of Sandoz Chemical Works, Inc., in the form of Neo Calglucon.

REFERENCES

1. Bowers, J. O., and Mingle, H. A. K.: The Additive Effect of Calcium and Digitalis, *J. A. M. A.* 106: 1151, 1936.
2. Lloyd, W. D. M.: Danger of Intravenous Calcium Therapy, *Brit. M. J.* 1: 662, 1928.
3. Golden, J. S., and Brams, W. A.: Mechanism of the Toxic Effects from Combined Use of Calcium and Digitalis, *Ann. Int. Med.* 11: 1084, 1938.
4. McGuigan, R. A., and Higgins, J. A.: The Influence of Calcium Salts on Digitalis Action, *J. Lab. and Clin. Med.* 23: 839, 1938.
5. Goldberg, S. J.: (a) The Use of Calcium Gluconate as a Circulation Time Test, *Am. J. Med. Sc.* 192: 36, 1936, and (b) Circulation Time as a Diagnostic Aid in Hyperthyroidism, *Ann. Int. Med.* 11: 1818, 1938.
6. Baer, S., and Slipakoff, B. G.: Measurement of Circulation Times and the Agents Used in Their Determination, *AM. HEART J.* 16: 29, 1938.
7. Berliner, K.: The Effect of Calcium Injections on the Human Heart, *Am. J. Med. Sc.* 191: 117, 1936.
8. Berliner, K.: The Effect of Calcium on the Heart, *AM. HEART J.* 8: 548, 1933.
9. Wolfe, J. B., and Bellet, S.: Cessation of Attacks of Auricular Paroxysmal Tachycardia by the Use of Calcium, *Ann. Int. Med.* 4: 795, 1931.
10. Walters, W., and Bowler, J. P.: Preoperative Preparations of Patients with Obstructive Jaundice—an Experimental Study of the Toxicity of Intravenous Calcium Chloride. Used in the Preparation of Patients, *Surg. Gynec., and Obst.* 39: 200, 1924.
11. Hoff, H. E., and Nahum, J. H.: An Analysis of the Cardiac Irregularities Produced by Calcium and Their Prevention by Sodium Amytal, *J. Pharmacol. and Exper. Therap.* 60: 425, 1937.
12. Nahum, L. H., and Hoff, H. E.: Effect of Calcium on the Digitalized Heart, *Proc. Soc. Exper. Biol. and Med.* 36: 860, 1937.
13. Gold, Harry, and Kurt, Nathaniel: Digitalis and Calcium Synergism, *Science* 86: 330, 1937.
14. Gold, Harry, and Edwards, Dayton J.: The Effects of Ouabain on the Heart in the Presence of Hypercalcemia, *AM. HEART J.* 3: 45, 1927.
15. Lieberman, A. L.: Studies on Calcium VI. Some Inter-Relationships of the Cardiac Activities of Calcium Gluconate and Scillaren-B, *J. Pharmacol. and Exper. Therap.* 47: 183, 1933.
16. Nyiri, William, and DuBois, Louis: Experimental Studies on Heart Tonics III. The Relationships of Calcium Ions, Hydrogen Ions and Digitalis, *J. Pharmacol. and Exper. Therap.* 39: 111, 1930.
17. Billigheimer, E.: Wirkung und Zusammenhänge von Calcium und Digitalis, *Klin. Wchnschr.* 8: 724, 1929.
18. Kraus, F.: Ueber die Wirkung des Calciums auf den Kreislauf, *Deutsche med. Wchnschr.* 46: 201, 1920.
19. Lentowitsch, A.: Elektrokardiogrammstudien über die Wirkung der Calciumsalze der Ringerschen Lösung aufs Herz., *Pflüger's Arch. f. d. ges. Physiol.* 147: 143, 1912.
20. Fröhlich, A., and Gussenbauer, R.: Die Wirkung der Erdalkalien auf das Elektrokardiogramm normaler und oxalatvergifteter Kaninchen, *Arch. f. exper. Path. u. Pharmacol.* 97: 61, 1923.
21. Bernstein, M., and Simkins, S.: The Use of Magnesium Sulfate in the Measurement of Circulation Time, *AM. HEART J.* 17: 218, 1939.

Department of Clinical Reports

INTRATHORACIC GOITER SIMULATING RIGHT-SIDED CARDIAC ENLARGEMENT*

CASE REPORT

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EXTRUSION and pedunculation of thyroid adenomata are not unusual. However, it is exceedingly rare that the pedicle is so long and extends so far into the mediastinum that the lower portion of the thyroid nodule is in contact with the diaphragm. In the case to be reported, the mediastinal extension of the nodular thyroid simulated right-sided cardiac enlargement in the roentgenogram of the chest. In a search of the literature we found reports of only two other such cases.^{1, 2}

REPORT OF CASE

B. B. V., a 51-year-old, white, married, American housewife, was admitted to the University of California Hospital on Jan. 3, 1938. She had had a goiter for thirty years, and right upper quadrant pain for two years.

When the patient was 21 years old, following her second pregnancy, she had become aware of a gradually progressive enlargement of the left side of her neck. After her third pregnancy, at the age of 23, a similar swelling had appeared on the right side. The enlargement of her neck had continued to increase until she entered the University of California Clinic. For several years before her entry she had had attacks of syncope, with loss of consciousness for an hour or longer. In the two years before entry, smaller tender nodules had appeared within the larger masses in her neck. Also, she had had attacks of pain in the right upper quadrant of the abdomen, radiating to the right costovertebral angle, to the right lower quadrant, and to the outer side of the right thigh. She had experienced some epigastric distress and eructations after eating fatty foods.

She had always lived in Modoc County, California. In childhood, she had had measles, mumps, chicken pox, and pertussis, and pertussis again at the age of 21 years. At the age of 40 years, "pneumonia" had complicated a miscarriage in the eighth month of gestation. The patient stated that she had had some nasal obstruction on the left side, and that her teeth were in poor condition. She had had hemorrhoids for many years. Menstruation had been irregular, with menorrhagia and metrorrhagia. There had been no significant changes in weight. She had had no accidents and no operations. She had been married at the age of 16 years, and had had 14 pregnancies, six of which terminated in miscarriages between the fifth and eighth months of gestation.

There was no familial history of goiter. One brother had idiopathic epilepsy.

On physical examination the patient was found to be a large, obese, well-developed, florid woman of 51 years, obviously uncomfortable and dyspneic. Her weight was 189 pounds. The pulse rate was 88, the temperature 37° C., and the respiratory rate 20 per minute. The skin was dry and wrinkled. The hair was normal in texture

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Received for publication Dec. 16, 1938.

and distribution. The nasal septum was deviated to the left. The tonsils were present and normal. Many teeth had been removed, and those remaining were carious. The thyroid was enlarged to about twenty or more times the normal size, was nodular, and extended substernally. The sternocleidomastoid muscles were pushed laterally and posteriorly. The trachea was displaced to the left. No thrill or bruit was heard over the thyroid. The thorax was emphysematous. The lungs were normal. The area of cardiac dullness was greatly increased. There was a soft, low-pitched, apical systolic murmur. The cardiac rhythm was normal. The blood pressure was 125/70. The peripheral arteries were thickened. The abdomen was obese. Examination of the spine showed a scoliosis to the left, senile kyphosis, and right-sided costovertebral tenderness. The cervix was patulous. There were a cystocele and rectocele. There were varicosities of both legs.

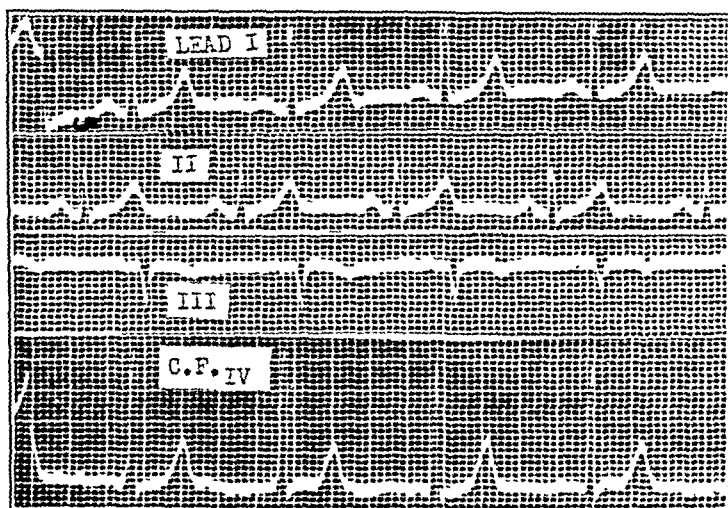


Fig. 1.—Electrocardiogram taken preoperatively.

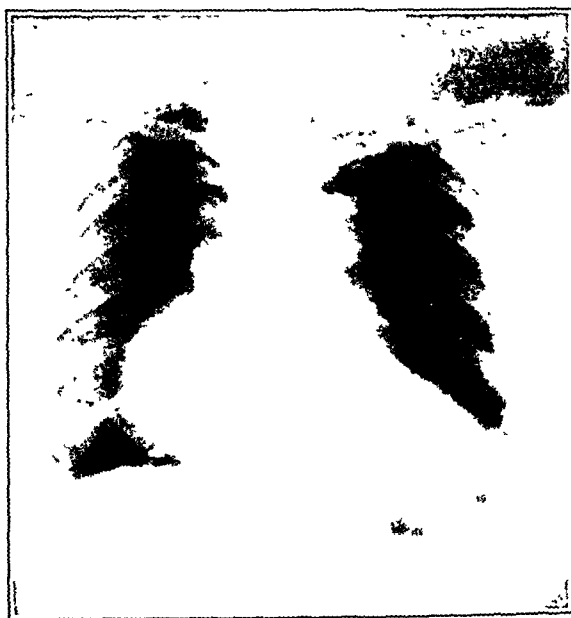


Fig. 2.—Posteroanterior roentgenogram of chest, taken preoperatively.

Laboratory Examination.—The urine was normal. The hemoglobin was 101 per cent (Sahli); the erythrocyte count 5,120,000; and the leucocyte count 9,250. The differential count showed 59 per cent polymorphonuclears, 31 per cent lymphocytes,

and 7 per cent monocytes. The Mosenthal test gave normal results. The electrocardiogram showed left axis deviation, a monophasic QRS_e, a high T₁, and slightly slurred QRS complexes and ST intervals, with a rate of 75 and normal rhythm. The electrocardiologist concluded that there was "no definite evidence of myocardial damage." A roentgenogram of the chest was interpreted by Dr. J. F. Huffman as follows: "The thyroid is greatly enlarged in the neck and extends downward substernally with its lower border overlying the heart, making it actually, as well as apparently, wider in the transverse diameter. The trachea is displaced forward in the neck and to the left substernally. There are a few calcifications on the left side of the gland in the neck."

On Jan. 12, 1938, a partial thyroidectomy, through the usual Kocher incision, was done by Dr. Harry Benteen and Dr. Leon Goldman. The portion of gland removed weighed 436 gm. The pathologic diagnosis by Dr. E. I. Bartlett was "thyroid adenomata." There was considerable hemorrhage during the thyroidectomy, and the patient showed signs of shock, but she was in fair condition when she was returned to the ward. At 10 P.M., on January 12, she received a transfusion of 600 c.c. of citrated blood. At 11 P.M., the respirations became labored, there was laryngeal stridor, and she was restless and cyanotic. Some skin clips were removed and several large blood clots evacuated. She died a few minutes later.



Fig. 3.—The thoracic viscera, showing relative sizes of the heart and intrathoracic goiter. The goiter has been cut across its upper portion. The organs have been placed as nearly as possible in the position in which they were seen when the chest cavity was opened.

The post-mortem examination was done fourteen and one-half hours after death by Dr. Nathan Rudo. The right side of the neck was found to contain little thyroid tissue, but was full of blood clots which, if liquid, would have amounted to 400 to 500 c.c. The left side of the neck showed less evidence of hemorrhage. It contained a large thyroid adenoma measuring approximately 10 by 9 by 7 cm. In the

right side of the mediastinum, another large, encapsulated adenoma, measuring 10 by 10 by 8 cm., hung from a pedicle with its tip touching the diaphragm. This mediastinal part of the thyroid was covered by a portion of the pleura, which formed part of the pedicle itself. There were no adhesions between this adenoma and the pericardium, but the two were seen to be in apposition when the chest was opened. The adenoma appeared to be about one-third again as large as the heart, and displaced that organ to the left. The parenchyma of the right lung was compressed and the alveoli were collapsed. The alveoli of the left lung were filled with precipitated serum. The gall bladder was normal.

On microscopic examination, some of the muscle bundles of the heart were seen to be large and fragmented and showed cross striation poorly; there was apparently some edema of the interstitial tissue. There was slight to moderate atherosclerotic degeneration of the aorta. The thyroid contained both large and small acini full of dark-staining colloid. The acini were lined with low cuboidal epithelium. The capsules of the thyroid adenomas consisted of dense fibrous tissue with calcification beginning in some areas.

DISCUSSION

Preoperatively, there was some doubt as to the diagnosis. Most of the roentgenologists thought that the heart was enlarged and that the thyroid extended only to the arch of the aorta. Lateral roentgenograms of the chest did not help in the diagnosis, and unfortunately no fluoroscopic examination was done, although this is a routine procedure in examining patients with goiters. In retrospect, this would have made possible an accurate clinical diagnosis.

It seemed impossible that the heart could be greatly enlarged when the electrocardiogram was so nearly normal. At the post-mortem examination the heart was found to be relatively normal in size, and the apparent enlargement of the cardiac shadow proved to be produced by the intrathoracic goiter. It is very unlikely that the degree of right ventricular hypertrophy indicated by the roentgenogram of the chest could have occurred without evidence of right axis deviation in the electrocardiogram and without electrocardiographic signs of myocardial damage.

Had we thought that the right lobe of the thyroid extended so low in the chest, the surgical approach would have been made by splitting the sternum. Only in this way would it have been possible to control the hemorrhage which ultimately caused the patient's death.

The mechanism of extension of the substernal adenoma was probably the growth of the gland in the plane of least resistance. The superior thoracic cavity was filled with goiter, and further growth was easier downward into the mediastinum. The fact that the pedicle of the thoracic goiter was connected directly with the goiter in the neck precludes the assumption that it arose from aberrant thyroid tissue in the mediastinum.

REFERENCES

1. Miller, Ralph Burquin: Large Intrathoracic Goiter, *Am. J. Roentgenol.* 40: 66, 1938.
2. Means, James H.: *Thyroid and Its Diseases*, p. 520, Philadelphia, 1937, J. B. Lippincott Company.

ARTERIAL OCCLUSION IN THE LEFT UPPER EXTREMITY OF A MONGOLOID IDIOT WITH CONGENITAL HEART DISEASE (TETRALOGY OF FALLOT)

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THE condition described herein is so unusual that it merits report. A mongoloid idiot with congenital heart disease (tetralogy of Fallot), who came to autopsy, showed a thrombus of the ductus arteriosus extending into the aorta, and the left common carotid, subclavian, axillary, and brachial arteries. Maude E. Abbott¹ says that "thrombosis in the patent ductus is a well-recognized condition, but the combination of a thrombosed ductus extending into the subclavian with or without congenital heart disease has not, as far as I know, been reported at all. Most of the cases of thrombosis have been reported under the title 'so-called aneurysm of the ductus Botalli.'" Abbott² states further that "the condition is chiefly of pathological interest, although its occasional rupture, and also the risk of embolism from the thrombus, increases its clinical significance. All the cases recorded are in infants, excepting that by Hebb."

REPORT OF CASE

A male infant of Italian parentage, three weeks old, was admitted to the Barnert Memorial Hospital Feb. 1, 1937. One day before admission it was noticed that the left upper extremity was pale and weak. The infant had been cyanotic from birth, refused to nurse, and progressively lost weight. For one week following birth the urine was red in color. Three siblings were alive and well, and one other child died at the age of two years with edema of the extremities.

Physical examination revealed a typical mongoloid idiot (Fig. 1), with generalized cyanosis which became more intense on crying. The infant was dehydrated and weighed 7 pounds. The temperature was 96° F. A profuse purulent discharge came from both eyes. The palms and soles were beefy-red and edematous. The left hand lay flaccid, and the baby, when stimulated, could move its left arm only at the shoulder. The pallor of the extremity was more or less sharply demarcated at the junction of the upper and middle thirds of the arm. The finger tips of the left hand were more cyanotic than those of the right. No pulse could be felt at the wrist or elbow. Examination of the heart showed a fairly loud systolic murmur, transmitted downward along the left margin of the sternum and best heard over the third intercostal space near the pulmonic area. The pulmonic second sound was accentuated. No thrill was palpable. The diagnosis was mongoloid idiocy, congenital heart disease, and arterial occlusion of the vessels of the left arm.

Laboratory Findings.—On Feb. 5, 1937, the hemoglobin was 126 per cent; the erythrocyte count 6,410,000; and the color index 0.98; no changes in the red blood cells were seen. The leucocytes totalled 15,150, with 68 per cent neutrophils, 30 per cent lymphocytes, and 2 per cent large mononuclear and transitional cells. The blood Wassermann reaction was negative. The urine showed a specific gravity of 1.017, a

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Received for publication Jan. 7, 1939.

trace of albumin, a few epithelial cells, a few leucocytes, and an occasional granular cast. A smear from the left eye showed Gram-positive bacilli, but no cocci or pus cells. A smear from the right eye showed a moderate amount of polynuclear leucocytes and Gram-positive bacilli. A roentgenogram of the heart was reported as showing nothing abnormal (Fig. 2).



Fig. 1.—Note mongoloid facies and flaccid and shrunken left upper extremity.



Fig. 2.—Roentgenogram of heart.

Course.—The dehydration on admission was relieved by hypodermoclyses of a 5 per cent solution of glucose in saline. Caffeine citrate, in doses of 1 grain, was given by mouth every four hours. Oxygen was administered through a nasal catheter. The general cyanosis persisted; the left extremity remained pale; the infant slept a great deal.

Each day the left hand became more shrunken, until, on Feb. 5, the terminal phalanges were mummified. Two days later the whole left hand was the seat of dry gangrene. A band of ecchymosis surrounded the left arm at the junction of the upper and middle thirds. During this time the infant's general condition remained surprisingly good. His purulent conjunctivitis improved, and he took his feedings fairly well, although his weight fell from 7 pounds to 6 pounds 5 ounces.

The temperature, which rose from 96° F. on admission to 101° F. on the fourth day, varied between this and normal until the eighth day, when it rose to 106° F. The following day it fell to 97° F., just before the infant expired. The pulse rate was 120 on admission, and fell and rose with the temperature. It ranged from 110 to 180. The respiratory rate ranged from 30 to 50. On February 9, the infant's cyanosis increased, his breathing became stertorous, and he died on Feb. 10, 1937.

Autopsy Report (Dr. Hans Wassing).—Post-mortem examination showed a cyanotic, emaciated infant with mongoloid features. There was a dry gangrene of the fingers of the left hand, and an early gangrene of the extremity as a whole. On opening the thoracic cavity there was an enormous venous congestion of the large vessels of the neck. The internal organs were markedly cyanotic. The lungs showed marked hypostatic congestion. Otherwise, there were no outstanding lesions in the internal organs except the heart. The skull was not opened. The heart showed a defect of the membranous portion of the interventricular septum. The aorta arose from both ventricles. The pulmonary valve was narrow and had two cusps; the pulmonary artery was narrowed. The ductus arteriosus and foramen ovale were both patent. In the upper part of the ductus there was a thrombus which extended into the ascending aorta, and the left common carotid, left subclavian, axillary, and brachial arteries.

SUMMARY

The case of a mongoloid infant with congenital heart disease (tetralogy of Fallot) is reported because of the development of an unusual complication, namely, a thrombosis involving the patent ductus arteriosus, the ascending aorta, the left common carotid artery, and the left subclavian, axillary, and brachial arteries. No similar condition, excepting thrombosis of the ductus Botalli, has been reported in the literature.

REFERENCES

1. Maude E. Abbott: Personal Communication.
2. Maude E. Abbott: Osler and McCrae's "Modern Medicine," Ed. 3, Vol. 4, 1927, p. 770.

Department of Reviews and Abstracts

Selected Abstracts

Lindner, E., and Katz, L. N.: The Relative Conductivity of the Tissues in Contact With the Heart. *Am. J. Physiol.* 125: 625, 1939.

Observations were made on sixteen nembutalized dogs in studying the effects of insulation of various regions around the heart on the voltage of the QRS of the standard limb-lead electrocardiograms. All animals were breathing normally with chests closed at the time records were taken. The following were the results obtained:

“Mock” operation had no appreciable effect on the strength of the peripheral electrical field of the heart.

Insulation between the lungs and the lateral surfaces of the heart produced no apparent change.

Insulation of the heart from the posterior muscle mass resulted in an approximate reduction of voltage of 34 per cent.

Insulation of the heart from the anterior chest wall reduced the voltage by 14 per cent.

Insulation of the heart from the diaphragm decreased the voltage by 25 per cent.

Ligation close to the heart of all the vessels of the larger circuit (except the coronary circuit) reduced the voltage by 10 per cent, while separating the cut ends of these vessels reduced the voltage 40 per cent.

By elimination of the other surfaces, therefore, the region immediately cephalad to the base of the heart carries roughly 27 per cent of the current generated by the heart to the body.

It is suggested that the heart itself, because of the absence of any effect on the electrocardiogram save that of decrease in voltage, must be an excellent conductor.

AUTHORS.

Andrus, E. Cowles, and Wilcox, Herbert B., Jr.: The Effects of Anaphylaxis, and of Histamine, Upon the Coronary Arteries in the Isolated Heart. *J. Exper. Med.* 69: 545, 1939.

Anaphylaxis in the isolated, perfused hearts of cats has been shown to be accompanied by a considerable, though transient, increase in coronary flow. This result is contrasted with that observed in the hearts of guinea pigs and rabbits in which the coronary arteries are constricted during anaphylaxis. Attention is directed to the fact that, in the hearts of these three species, the effects of anaphylaxis and of histamine are qualitatively parallel.

The characteristic anaphylactic response in the isolated hearts of guinea pigs has been evoked: (a) in the organs removed from immune animals, (b) by each of two antigens (horse serum and egg albumen) under conditions of double sensitization, and (c) upon exposure of the hearts of passively sensitized animals to the type-specific polysaccharide of the pneumococcus.

It is evident that, among the effects of anaphylaxis upon smooth muscle in various organs, there must be considered that upon the coronary arteries.

AUTHORS.

Mainzer, F., and Krause, M.: The Electrocardiogram of the Dog After Phlorrhizin Poisoning. *Cardiologia* 2: 129, 1938.

Phlorrhizin which inhibits phosphorylation causes an increase in QRS with splintering and inconstant S-T and T changes. These changes are not related to glycosuria and persist after glycosuria has passed off. They appear within a few hours and are not due to left ventricular hypertrophy which follows chronic poisoning. The changes are reversible. The changes are attributed to a disturbance in carbohydrate metabolism. They resemble changes in beri beri.

KATZ.

Rothberger, C. J., and Sachs, A.: Is There a Positive Inotropic Action of Cholin Derivates on Auricular Strips From Warm-Blooded Animals? *Cardiologia* 2: 71, 1938.

On occasion, instead of a negative, a positive, inotropic effect on these auricular strips was found. This occurs only with very small doses of neostigmine or its derivatives. This positive effect is reversible on washing and is abolished by atropine.

KATZ.

Zothe, H.: The Action of Strophanthin in Peripheral Circulatory Disturbances. *Ztschr. f. Kreislaufforsch.* 30: 889, 1938.

Strophanthin, in therapeutic doses intravenously, leads to an improvement of the depressed muscular contraction caused by peripheral circulatory disturbances. This improvement is attributed to an improved O_2 utilization, not caused by improvement in flow but by increased avidity of the tissue for O_2 . This suggests a new therapeutic use of strophanthin.

KATZ.

Deppe, B., and Diefenhardt, H. H.: The Resemblance in Man of Circulatory Readjustment During Exercise to That Following Adrenaline Intravenously. *Ztschr. f. Kreislaufforsch.* 31: 1, 1939.

Utilizing data concerning the duration of systole, diastole, and cycle, together with that on pulse wave velocity, systolic, diastolic, and pulse pressure, and the data on the effective cross section of the elastic reservoir (Suter's tables), they have calculated heart stroke volume, volume elasticity, and peripheral resistance of the circulatory system.

A remarkable resemblance in the character of the response of these determined and calculated variables was found to exist between exercise and adrenaline action. The pattern of the two shows the same individual variation amongst the subjects studied.

KATZ.

Puddu, V.: Electrocardiographic Alterations After Effort in Normals and Patients With Angina Pectoris, With Special References to the Chest Lead. *Cardiologia* 2: 183, 1938.

Ten normal and fourteen angina patients were studied. Only slight changes were noted following exercise in the normal subject; especially common was the fact that S-T may become depressed about 1 mm.

In anginal patients, the electrocardiogram may remain unchanged, but usually S-T is depressed in the limb leads and the T wave in these leads may become diphase or inverted. In the chest lead (new terminology) S-T may become

noticeably depressed and T diphasic, inverted or small. In some, the electrocardiogram comes to resemble curves in myocardial infarction. Sometimes changes occur only in limb leads, and sometimes only in chest leads.

KATZ.

Ayman, David, and Goldshine, Archie D.: The Breath-Holding Test. Arch. Int. Med. 63: 899, 1939.

Holding the breath in quiet expiration, with the nose and mouth closed, for twenty seconds is a simple standard stimulus of blood pressure. Hypertension and hyporeactors can be determined by this method. The test is simpler and furnishes a somewhat greater stimulus than the cold pressor test.

AUTHORS.

Thomson, W. A. R.: Potassium and the T Wave of the Electrocardiogram. The Lancet 1: 808, 1939.

A case of Addison's disease is reported in which a fall in the level of the serum potassium was accompanied by a diminution in the height of the T wave in the electrocardiogram.

Five other cases are described in which a rise in the level of the serum potassium was accompanied by an increase in the amplitude of the T wave, followed in some of them by a decrease in the amplitude of the T wave when the level of the serum potassium fell again.

It is suggested that there is a correlation between the concentration of the serum potassium and the height of the T wave.

AUTHOR.

Laubry, Charles, Soulie, P., and Laubry, P.: Diagnostic Value of a Triphasic Rapid Wave in Angina Pectoris and Coronary Syndrome. Arch. d. mal. du coeur. 32: 337, 1939.

Triphasic QRS, of any type, should be systematically examined, not only in Lead III, but also in the other leads (including chest leads). Triphasic QRS occurred fifty-one times in 2,000 tracings.

Coronary occlusion.—Fifteen of the fifty-one patients had coronary occlusions. Amongst a sample of ninety patients with coronary occlusion, 12 per cent had triphasic QRS. Triphasic QRS was often associated with other evidence of coronary occlusion. In the fifteen cases, in contradistinction to the other forms of heart disease, the triphasic QRS was seen in one lead only, though this might be any lead. Triphasic QRS₂ was often associated with the presence of Q_r. When absent in the standard leads, it might occur in the chest lead. When the QRS had become triphasic from acute coronary occlusion, the triphasic quality tended to disappear during the follow-up period.

Angina pectoris.—Thirteen of the fifty-one patients had angina pectoris. In this group the QRS was often triphasic in several leads of the same tracing. If this occurred in Leads I and III, the R waves usually pointed away from each other. Once the complexes were triphasic in all three standard leads.

Fourteen patients had other forms of organic heart disease (hypertension, aortitis, cor senile). Thus, 82 per cent of the patients with triphasic QRS complexes had other evidence of organic degenerative heart disease. This finding is in keeping with the general experience of the literature.

Four others had valvular heart disease. In only five cases (10 per cent) was there no evidence of organic heart disease.

JENSEN.

Schlomka, G., and Neuking, P.: **Studies of Sinus Arrhythmia. X. In Patients With Labile Circulation.** *Ztschr. f. Kreislaufforsch.* 30: 504, 1938.

Sinus arrhythmia was present in these patients, and this was prominent even in those with the faster resting heart rates. The practical value of sinus arrhythmia in evaluating the state of the heart is apparent.

KATZ.

Herles, F., Lukl, P., Prusik, B., and Sikl, H.: **Location of Bundle Branch Block.** *Cardiologia* 2: 1, 1938.

A detailed report of three cases of left bundle branch block with autopsy check is presented. In one the right bundle branch was found intact. The electrocardiograms in all were of the common type.

KATZ.

Lian, C., and Pinchenzon, B.: **Auricular Tremulation.** *Cardiologia* 2: 56, 1938.

A lead connecting the manubrium to the fifth intercostal space parasternally was found useful for studying auricular waves. The authors refer to a state intermediary between flutter and fibrillation which they call tremulation. This can be recognized only in the precordial lead described. This is distinguished by regularity in the auricular wave but with some variation. Digitalis in large doses converts tremulation to fibrillation.

KATZ.

Hadorn, W., and Frey, W.: **The Strophanthin Electrocardiogram.** *Cardiologia* 2: 87, 1938.

Typical digitalis deformities following strophanthin in therapeutic doses were found in two cases. Similar changes were noted in rabbits. Glucose given simultaneously had no effect on the action of strophanthin, nor did atropin have any influence.

KATZ.

Ewert, B., and Kallos, P.: **Electrocardiographic Studies in Experimentally Produced Asthma in Guinea Pigs.** *Cardiologia* 2: 147, 1938.

Asthma attacks were produced in sensitized guinea pigs by inhalation of atomized antigens. Inhalation of finely divided histamine or acetylcholine solutions also produces asthma in healthy non-sensitized guinea pigs. The anatomical findings in this latter group differ from the former. During the allergic and drug asthmas, electrocardiographic changes are seen including T wave alterations, disturbances of rhythm and conduction, and typical changes such as seen in myocardial infarction. These quickly return to normal after the attack. Histologically, no myocardial abnormalities are found. The electrocardiographic changes are therefore attributed to coronary spasm.

KATZ.

Hegglen, R.: **Systole in Insulin Shock and Diabetic Coma.** *Cardiologia* 2: 170, 1938.

In diabetic coma, in insulin shock, and following large doses of insulin in the treatment of the former conditions, electrical systole is lengthened and mechanical systole shortened. This demonstrates that electrical and mechanical events in the heart are not synchronous.

KATZ.

Lepeschkin, E. W.: The Electrocardiogram in Experimental Coronary Insufficiency, Hemorrhage, and Reinfusion. *Cardiologia* 2: 236, 1938.

Experiments were done on thirty-two dogs. Following hemorrhage the heart speeds up, then slows, and then stops because of S-A block. Then ectopic beats occur, and sinus rhythm becomes re-established with A-V block. Often there is ventricular fibrillation. At first the relative duration of electrical systole is increased but later decreased. Before A-V block develops the P-R is shortened. QRS is first shortened and later prolonged. Monophasic-like QRST complexes appear in severe stages.

Transfusion of the dog's own blood may reverse these processes.

KATZ.

Wullenweber, G.: Angina Pectoris Caused by Hematomyelia. *Ztschr. f. Kreislaufforsch.* 31: 16, 1939.

A case report of traumatic hematomyelia in a 26-year-old male who developed precordial pain on exertion a year after injury is presented. There was no evidence of heart disease, and nitroglycerine was without effect. The spinal cord injury involved C6 to T3. The case illustrates the importance of nerve pathways in the genesis of angina.

KATZ.

Blahd, Margery, Frank, Ira, and Saphir, Otto: Experimental Endocarditis in Dogs. *Arch. Path.* 27: 424, 1939.

Endocarditis was produced in 40 per cent of twenty-five dogs by simply injecting intravenously hemolytic streptococci isolated from a dog. In four dogs endocarditis was produced with a single injection. It is suggested that the use of a virulent strain isolated from the same species contributed to the positive results. It is concluded that numerous factors may be involved in the development of endocarditis. However, the presence of these several factors is not essential. For virulent organisms, per se, may cause acute bacterial endocarditis in a previously healthy animal.

AUTHORS.

Welty, J. W.: A Necropsy Survey of Cardiovascular Syphilis With Particular Reference to Its Decreasing Incidence. *Am. J. M. Sc.* 197: 782, 1939.

Syphilitic cardiovascular disease was encountered in 6.93 per cent of 15,000 autopsies at the Philadelphia General Hospital. The incidence of syphilitic aortic regurgitation was 1.44 per cent and of syphilitic aneurysm 1.28 per cent.

Statistical data concerning sex, color, and age are given.

Syphilitic cardiovascular diseases, in all forms and as a cause of death, show a definitely decreasing incidence during the 10-year period, 1927 to 1937.

It is believed that the decreasing incidence may be explained by modern methods of therapy.

AUTHOR.

Zweifach, Benjamin William: The Character and Distribution of the Blood Capillaries. *Anat. Record.* 73: 475, 1939.

Studies on living blood capillaries in the frog and mouse by a micromanipulative technique reveal the presence of two types of capillaries. The architecture of the capillary system is such that the two types map out characteristic anatomical units, the arrangement of which is an important factor for the regulation of the local distribution of blood.

One type of capillary, containing muscular elements, is a direct extension of the arteriole and continues through to the venule. This capillary has been designated

the arteriolo-venular or a-v bridge. This capillary conveys an active flow of blood, even when the tissues are in a resting or anemic state. The other type of capillary is purely endothelial and is termed "non-muscular or a true capillary" and is an offshoot from the a-v capillary. A number of true capillaries are present in each capillary system. Only one a-v bridge is present in each such unit.

Functionally, under resting conditions blood is flowing only through the a-v bridge. With increased venous congestion the side pathways or true capillaries are opened, and the flow is redistributed. With return to basal conditions the true capillaries either collapse or are simply devoid of circulating blood, only the a-v bridges containing a continuous flow.

NAIDE.

Williams, J. R., Jr., Harrison, T. R., and Grollman, A.: A Simple Method for Determining the Systolic Blood Pressure of the Unanesthetized Rat. J. Clin. Investigation 18: 373, 1939.

A method is described for measuring the systolic blood pressure in the tail of the intact unanesthetized rat, which when modified as to size, is suitable for use on other animals.

AUTHORS.

Houssay, B. A., Fasciolo, J. C., and Taquini, A. C.: Mechanism of Arterial Hypertension of Renal Origin. Rev. argent. de cardiol. 5: 291, 1939.

The ischemic kidney secretes a vasoconstrictor substance which causes a permanent hypertension. This substance is easily demonstrable; 1) because it exists in the blood of the renal vein; 2) because an ischemic kidney from a hypertensive dog grafted in the neck of a recently nephrectomized dog causes, in a few minutes, a rise in the arterial pressure of the latter.

This substance has a constrictor action on the perfused vascular systems of both the toad and the dog. The normal kidney does not produce such a substance for its venous blood has no constrictor effect, and, if grafted, it does not alter the blood pressure of the receptor.

The vasoconstrictor substance has its origin in the kidney and produces its blood pressure raising effect independently of the adrenals, for the graft of an ischemic kidney raises the blood pressure of a recently adrenalectomized dog. Various authors have observed that adrenal insufficiency causes a fall in the blood pressure of a dog made hypertensive by renal ischemia, but it is not yet clear if this is due to the inability of the kidney to produce the hypertensive substance, or to the non-reactivity of the vascular system to this substance.

Healthy renal tissue protects in a way still unknown from the hypertensive action of the ischemic kidney. This hypertensive action is not affected by renal denervation or by resection of large portions of the vasomotor nervous system. Hypertension is independent from uremia.

After complete renal ischemia, a vasoconstrictor substance also appears for, 1) when the circulation through the kidney is re-established, the blood pressure rises immediately. 2) the renal venous blood has a vasoconstrictor effect and, 3) the graft of this kidney in the neck of a normal dog produces a rapid rise of blood pressure. It is still unknown if the vasoconstrictor substance of the completely ischemic kidney, which may be considered as dead, is similar to that of the ischemic kidney which lives and functions continually during several months.

It is necessary to find sure and sensitive methods which would enable us to find the vasoconstrictor substance of renal origin in the peripheral blood of hypertensive subjects.

AUTHORS.

Bisgard, J. Dewey: Relation of Hyperthyroidism to Hypertension. Arch. Int. Med. 63: 497, 1939.

As a physiologic response to hyperthyroidism, the systolic blood pressure is usually slightly or moderately elevated. It recedes to the normal level with relief of hyperthyroidism.

In a series of 265 cases studied, hyperthyroidism was associated with true essential hypertension in approximately 8 per cent and with elevations of the systolic pressure above the physiologic level (above 150 mm. of mercury) in 30 per cent. On the basis of changes of blood pressure following relief of hyperthyroidism, two types of cases are discernible: (1) cases with fixed or established essential hypertension, in which the blood pressure and the course of the vascular disease are not significantly influenced by relief of hyperthyroidism and, (2) cases with latent or labile essential hypertension, in which the blood pressure shows considerable reduction after relief of hyperthyroidism or approaches a normal level and maintains this level for a long period. In some cases of the second type the pressure is observed subsequently to ascend. In these cases there is excessive response in blood pressure to exercise and to the cold pressor test of Hines and Brown. It is suggested that the relation of hyperthyroidism to hypertension in these cases is provocative, that hyperthyroidism merely precipitates or exaggerates hypertension which is latent.

It is further suggested that in both types there is arteriolar disease, differing only in degree. In the first type the disease is more advanced, rendering the vascular bed inadequate for even a normal volume of blood flow. In the second type the disease may be designated as pretensive hypertension, which progresses to the condition of the first type with the advance of time.

AUTHOR.

Goldblatt, Harry, Kahn, Joseph R., and Hanzal, Ramon F.: Studies on Experimental Hypertension. The Effect on Blood Pressure of Constriction of the Abdominal Aorta Above and Below the Site of Origin of Both Main Renal Arteries. J. Exper. Med. 69: 649, 1939.

Constriction of the abdominal aorta just above the site of origin of both main renal arteries has little or no immediate effect on the blood pressure above the site of the clamp (carotid, systolic, or mean pressure), but in about twenty-four hours, hypertension develops. Below the site of the clamp, the immediate effect is the lowering of the femoral mean pressures. As the carotid systolic pressure becomes elevated, the femoral mean pressure also begins to rise and, in some animals, eventually reaches a level higher than normal, despite great constriction or even occlusion of the abdominal aorta.

Constriction of the aorta just below the origin of both main renal arteries has no significant effect on the blood pressure (carotid, systolic, or mean pressure) above the site of the clamp. Below the site of the clamp, the blood pressure falls and tends to remain down, or at most returns to the preoperative level.

The uremic, convulsive (malignant or eclamptic) phase of hypertension, with renal excretory insufficiency and degenerative, necrotizing, and inflammatory arteriolar lesions in many organs, has been produced by suddenly constricting to a great degree the abdominal aorta just above the origin of both main renal arteries. The presence of renal excretory insufficiency in the animals that develop hypertension is directly dependent upon the degree of constriction of the abdominal aorta, and especially the rapidity with which it is produced.

Hypertension following the constriction of the abdominal aorta just above the origin of both main renal arteries, whether or not accompanied by renal excretory insufficiency, is of renal origin.

AUTHORS.

Plenczner, A.: Comparison of Hypertension in Athletes and Non-Athletes. *Ztschr. f. Kreislaufforsch.* 30: 793, 1938.

The frequency and appearance of hypertension is similar in the two groups. The development of sinus bradycardia and increasing vital capacity with training occurs in both.

KATZ.

Harrison, C. V.: The Effect of Sympathectomy on the Development of Experimental Arterial Disease. *J. Path. and Bact.* 48: 353, 1939.

To test the effect of relaxation of the vessel wall on the development of experimental arterial disease, a series of rabbits were subjected to unilateral lumbar sympathectomy and subsequently fed with large doses of cholesterol in oil. A control group received similar cholesterol treatment but no operative interference. The vascular lesions on the sympathectomized side were more severe than on the opposite side. In the control animals there was no significant difference between the two sides. These results were confirmed by chemical estimation of the cholesterol in the excised vessels. It is concluded that sympathetic paralysis enhances the effect of cholesterol in producing vascular lesions. This experiment lends support to the hypothesis that atheroma is in part due to weakness of the underlying media.

NAIDE.

Bouvrain, Yves: Contribution to the Study of the Respiration of Cardiacs. Monograph, Louis Arnette, Paris, 1938.

This is a doctor's thesis written under the direction of Professor Laubry. After having discussed in detail the literature on the subject, she reports 107 experiments on the effect of effort on the oxygen consumption in health and in cardiac disease. The average results are tabulated as follows:

NUMBER OF CASES	CATEGORY	BASAL METABOLIC RATE	RATE DURING FIRST 3 MIN. FOLLOWING EFFORT	RATE DURING SECOND 3 MIN. FOLLOWING EFFORT
20	Controls	+ 2.15	+16.20	+ 2.50
11	Various forms of heart disease compensated	+ 9.00	+17.10	+ 5.00
19	Various forms of heart disease decompensated	+25.90	+41.30	+ 8.60
17	Hypertension compensated	+21.60	+26.00	+ 5.06
12	Hypertension decompensated	+25.70	+41.80	+11.00
21	Mitral heart disease compensated	+ 3.60	+22.00	+ 4.50
11	Mitral heart disease, pulmonary symptoms only	+ 1.80	+58.00	+19.50
16	Mitral heart disease, decompensated	+10.90	+30.60	+11.90

The effort tolerance test consisted in the two steps designed by Master and was modified according to his directions to fit individual cases. The average values, though no doubt significant, are impaired by a rather large scatter of the findings.

The basal metabolic rate among the patients with various forms of compensated heart disease was somewhat higher than among the controls, but oxygen consumption after effort was about the same. The average basal metabolic rate of a similar group with decompensated heart disease was much higher, though it included

patients with normal or even low basal metabolic rates. The increase bore no certain relation to the degree of failure. The oxygen consumption following effort was markedly increased. The highest oxygen consumption after effort occurred in the patients with the highest basal metabolic rate, though this was not an absolute rule.

Among patients with compensated hypertension the average basal metabolic rate was increased, though it was normal in some cases. The group included no cases of clinical hyperthyroidism. The hypertensive patients with high basal metabolic rates differed in no other way from the others. The oxygen consumption was increased after effort, but the increase bore no fixed relation to the basal metabolic rate. The patients with decompensated hypertension behaved practically like the patients with various forms of decompensated heart disease.

One patient with advanced hypertension had paradoxical findings:

His basal metabolic rate was +79, but following effort the rate of oxygen consumption fell to -30 for both periods of observation. Unfortunately the test was not repeated for the patient died two days later from a coronary infarct. The author thought that the hyperpnea following effort had been so severe as to prevent adequate gas exchange.

The findings among patients with compensated mitral heart disease were almost normal. A group with pulmonary symptoms had the lowest average basal metabolic rate of any group, but by far the highest oxygen consumption after effort. The author attempts to explain this by the mechanical obstruction to the blood flow caused by the stenosis, which during effort prevents a sufficient increase to meet the increased oxygen requirements. In decompensated mitral disease both the basal metabolic rate and the oxygen consumption after effort were increased.

The blood velocity was measured by the ether and by the saccharin methods, but proved of little value. In several cases with mitral disease and pulmonary embarrassment, the results were normal, only once was the time markedly prolonged. The circulation rate was not affected by the state of the pulmonary circulation, but rather by general decompensation.

As there is no definite relation between the degree of increase in oxygen consumption and degree of heart failure, the practical value of the test is limited. Even in the presence of marked heart failure, may the oxygen consumption be normal.

JENSEN.

McGuire, Johnson, Shore, Rose, Hauenstein, Virgil, and Goldman, Fred: *Influence of Exercise on Cardiac Output in Congestive Heart Failure*. Arch. Int. Med. 63: 469, 1939.

The influence of similar measured exercise on the cardiac output of five normal subjects, four patients with compensated cardiac disease and five patients with cardiac decompensation has been determined.

In the normal subjects a considerable increase in cardiac output with exercise occurred, the average increase being 2.07 liters per minute.

In the patients with compensated cardiac disease the increase in cardiac output was moderate, the average increase being 1.21 liters per minute.

In the patients with congestive heart failure the increase in cardiac output with exercise was small, the average increase being 0.75 liter per minute.

These data suggest that in patients with severe cardiac decompensation under the conditions of these experiments the cardiac output is not increased with effort to the same degree as it is in normal persons and that relative inability to increase the cardiac output may have an important bearing on the pathogenesis of congestive heart failure.

AUTHORS.

Day, Richard, and Klingman, Walter O.: The Effect of Sleep on Skin Temperature in a Case of Acrocyanosis. *J. Clin. Investigation* 18: 271, 1939.

A case of acrocyanosis in a 6½-year-old girl is described. In sleep, her hands and feet became warm and red; and under these conditions the hands responded in a parallel way with the rest of the body to warm and cold foot baths. Local cooling of the palm of the hand did not induce vasoconstriction when she was asleep. Microscopic observation of the capillaries at the base of the nails showed sluggish flow of blood and dilation of the venous side. These observations seem to support the contention of Lewis that in acrocyanosis the primary fault is vasoconstriction of the arterioles. However, the predominant influence of sleep over thermal influences on the condition of this patient's hands points to abnormal vasomotor tone of central origin as the primary cause, rather than local sensitivity to cold such as was demonstrated in their cases by Lewis and by Pearse. Further evidence of sympathetic nervous system dysfunction was noted in a peculiar blotchiness of the skin during spells of anger. Spasm of the pylorus, which was demonstrated radiologically on one occasion, constituted a possible cause of her periodic episodes of vomiting, and presented further evidence of widespread sympathetic abnormality.

AUTHORS.

Smith, H. W., Rovenstine, E. A., Goldring, W., Chasis, H., and Ranges, H. A.: The Effects of Spinal Anesthesia on the Circulation in Normal, Unoperated Man With Reference to the Autonomy of the Arterioles, and Especially Those of the Renal Circulation. *J. Clin. Investigation* 18: 319, 1939.

Twenty-one normal unoperated subjects have been observed before and during spinal anesthesia. In eighteen of these subjects sensory anesthesia was established up to T5, and in three subjects to above T1. That the anterior roots or sympathetic rami have been effectively blocked has been demonstrated by the abolition of the typical reflex responses to hypercapnia, anoxemia, and gravity.

Anesthesia to levels considerably above those at which the efferent sympathetic paths to the kidneys emerge from the cord does not produce renal hyperemia, nor does it have any other consistent effect upon the renal circulation. It is concluded that the tone of the renal arterioles is normally maintained by autonomous, intrinsic activity of the peripheral vascular apparatus and is not dependent upon tonic activity of the central nervous system.

Normal blood pressure may be maintained in normal, unoperated subjects with sensory anesthesia at spinal levels (T5 or higher) above those at which the highest vasoconstrictor fibers emerge to the splanchnic viscera and legs. In those instances in which the arterial pressure is reduced, the systolic pressure falls more than the diastolic, the latter being usually maintained at essentially normal levels. There is at no time the hemodynamic picture to be expected from arteriolar dilatation; rather the decrease in blood pressure is such as is to be expected in consequence of a decreased cardiac output in the face of an unchanged arteriolar bed. That the cardiac output is actually decreased is indicated by measurements available in the literature. This decreased cardiac output results from decreased stroke volume, the latter resulting from postarteriolar dilatation and decreased venous pressure. The postarteriolar dilatation can be explained in terms of dilatation of capillaries, venules, and veins in consequence of skeletal muscle paralysis, without positing tonic sympathetic activity to these circulatory channels. Possibly some further venous embarrassment is occasioned by paralysis of the abdominal and thoracic muscles, and, in some instances, by acute dilatation of the spleen. Dilatation of the arterioles of the skin, the only region for which there is indubitable evidence of sympathetic tonic activity in man, probably operates against the development of hypotension by contributing to the maintenance of venous pressure.

It is inferred that (like the renal arterioles) the arterioles of the other splanchnic viscera and probably the skeletal muscles possess sufficient autonomy to maintain a normal blood pressure after denervation, providing the method of denervation is not such as to precipitate severe circulatory disturbance. It is a corollary of this conclusion that there is normally negligible tonic activity in the sympathetic vasomotor paths.*

The peripheral vasomotor system in man under spinal anesthesia is highly resistant to hypercapnia and anoxemia, which precipitate circulatory collapse in the anesthetized sympathectomized dog and cat and in the anesthetized cervical dog by dilating some as yet undetermined portion of the vascular bed.

Evidence bearing on the tonic activity of the vasomotor system, as obtained from the sympathectomized dog and cat, the cervical dog, and the dog under spinal anesthesia, has been critically reviewed, and it has been pointed out that most of this evidence suffers from having been obtained from anesthetized animals, and reasons have been given for its inadequacy.

It may be emphasized that our conclusion regarding the absence of important tonic activity in the sympathetic vasomotor paths to the arterioles generally, and to the kidneys especially, refers only to normal man in the resting, basal condition, and in the supine position. It remains to be determined to what extent sympathetic activity may be evoked by traumatic excitation, by assumption of the upright posture, by excitement, in hypertensive disease, etc. Investigation of these questions relative to the kidneys is now in progress.

AUTHORS.

Naide, Meyer: The Use of Vitamin B₁ in Rest Pain of Ischemic Origin. *Am. J. M. Sc.* 197: 766, 1939.

Vitamin B₁ was given intravenously in doses of 100 mg. to ten patients with ischemic neuritis or rest pain of ischemic origin. Seven obtained complete relief of pain; two patients obtained partial relief, and one failed to obtain any relief. Pain was relieved only as long as vitamin B₁ was administered parenterally. Maintenance amounts of vitamin B₁ (20 to 100 mg. once or twice a week) were required to keep patients free from pain as long as the vascular condition remained unchanged.

Gangrene, ulcers, and objective neurologic changes were not improved by vitamin B₁.

Vitamin B₁ does not supplant the usual methods of treating peripheral vascular disease but is worthy of clinical trial in patients with refractory pain. Measures designed to increase peripheral circulation should always be used in these patients.

Vitamin B₁ was used intravenously in two patients with intermittent claudication and in normal individuals under conditions of experimental ischemia with equivocal results.

AUTHOR.

Master, Arthur M., Jaffe, Harry L., and Dack, Simon: The Drug Treatment of Angina Pectoris Due to Coronary Artery Disease. *Am. J. M. Sc.* 197: 774, 1939.

A study has been made of the effect of sixteen drugs, including a placebo, milk sugar, on angina pectoris due to coronary artery disease. The drugs included several xanthine derivatives, alcohol, sedatives such as phenobarbital, chloral, and bromides, the nitrites, a tissue extract, digitalis and two narcotics, codeine and dilaudid.

No drug was found to exert any specific effect on the anginal syndrome, for the best results were obtained with a placebo, and the number of patients improved ranged between 15 and 30 per cent for all drugs.

No drug was consistently successful in a significant number of cases. Some patients were helped by all drugs, others by none.

The beneficial effects attributed to many drugs in the past may be explained on the basis of insufficient consideration of the significance of the natural course of the anginal syndrome, and particularly, of psychologic factors, in determining the degree of pain. The mildness or severity of the anginal syndrome is often directly dependent on the emotional status of the patient at the time, regardless of the degree of coronary artery disease.

It is concluded that drugs should play a minor role in the treatment of angina pectoris. Instead the importance of such measures as rest, dietary restriction, and minute attention to the mental and emotional status of the patient, is emphasized.

AUTHORS.

Mulinos, Michael G., Shulman, Israel, and Mufson, Isidor: On the Treatment of Raynaud's Disease With Papaverine Intravenously. Am. J. M. Sc. 197: 793, 1939.

The vascular status of the hands of five patients with Raynaud's disease has been studied.

Treatment with histamine iontophoresis to the hands and papaverine hydrochloride intravenously in doses from 60 to 120 mg. three times a week has led to a) an objective increase in the vascular bed volume and the rate of blood inflow of the hand; b) a complete alleviation of the syncope, cyanosis, and pain from exposure to cold; c) the healing of trophic lesions when these were present.

No addiction and little cerebral depression occurs from the papaverine, despite long continued treatment (6 to 8 months).

AUTHORS.

Kramer, David W.: Intermittent Venous Compression in the Treatment of Peripheral Vascular Disorders. Am. J. M. Sc. 197: 808, 1939.

Periodic venous compression is offered as another method in treatment of peripheral vascular disease. It is based on logical principles, and investigations have shown that it does produce a beneficial effect upon the circulation.

A series of 103 patients were observed, totalling about 1,500 treatments. The usual run of vascular disorders were included, except the vasoneuroses and Raynaud's disease groups.

The results upon Buerger's disease and diabetics were average, 66.6 per cent being benefited. The arteriosclerotic group was disappointing, favorable results being obtained in only 60 per cent.

Phlebitis constituted the largest series, with thirty-three patients. Vasospasm was a common occurrence in these cases. The analysis showed that 72.8 per cent were favorably influenced.

Collectively, seventy patients (68 per cent) of the 103 in the series were benefited. Because of its favorable influence upon various vascular disturbances and because of its broader application, we consider intermittent venous compression a desirable addition and adjunct in the treatment of peripheral vascular diseases.

AUTHOR.

ON ELECTROCARDIOGRAPHIC CHANGES IN HEALTH AND DISEASE DURING EXPERIMENTAL ANOXEMIA: By Kaj H. Larsen, Iltmangel, Copenhagen, 222 pages, 1938.

This is a study of the effect of anoxemia, produced by the inhalation of 9 vol. per cent O_2 , and of effort, on the electrocardiogram. The work is of the highest order. The technique, especially the electrocardiographic procedure, is fully described. Also, the literature is very completely discussed.

The author states that anoxemia and effort, under standardized conditions, will so frequently produce characteristic changes in the electrocardiogram in patients with heart disease that these functional tests have real diagnostic value. He believes that with proper precautions the tests carry no risk.

The reviewer can only praise the excellence of this work, and accept it as a real addition to cardiologic knowledge. But the study includes only fifty-six tests on patients with coronary disease, and one death from angina pectoris, following an effort test, has been reported. I know of another. There is some evidence that anginal attacks may in themselves be fatal. Therefore, it is questionable whether any test involving the production of anoxemia in a patient with a damaged heart, often with concomitant precordial pain, will ever gain general acceptance.

Normal Persons.—Twenty normal persons were examined. P_2 became higher in eighteen, was unaltered in one, and lowered in one. There was a general, though not universal, tendency for the R waves to become lower. The T waves were lowered, but never inverted. Q-T₂ was shortened. The rate was increased, on an average, by 40 per cent. The S-T segment was not lowered more than 1 mm. The findings were statistically examined by Dr. G. Rasch, and normal standards were established.

Arteriosclerotic Heart Disease.—The author attributes all angina pectoris to myocardial anoxemia, although the actual mechanism whereby this can be produced may vary.

Among seventeen patients with "coronary angina pectoris," thirteen showed abnormal electrocardiographic changes during induced anoxemia, mostly depression of the S-T segments exceeding 1 mm., and partial or total inversion of T waves. Electrocardiographic changes which were present before the test became accentuated. Four patients who showed no electrocardiographic changes during anoxemia did so with effort.

While the tests in many cases produced precordial pain, there was no definite relation between the electrocardiographic changes and the pain. Either might occur without the other, or, if they occurred together, the onset and cessation might not coincide. The electrocardiographic changes were not prevented by previous administration of nitroglycerin.

The changes are not pathognomonic of coronary disease, for they may also occur in patients with rheumatic heart lesions, certain endocrine disorders, and severe anemia.

Effort (in the form of standardized bicycle tests) does not normally produce significant lowering of the S-T segment, or render the T waves diphasic or inverted, but in the author's series such changes occurred commonly in patients with coronary disease, including some in whom the electrocardiograms had not been changed by anoxemia.

In four out of sixteen patients with arteriosclerotic heart disease, but without angina pectoris, the electrocardiograms were changed by anoxemia. The changes were not associated with precordial pain.

In ten patients with attacks of pain in the chest, but without objective evidence of heart disease, anoxemia produced no changes in the electrocardiogram. However, absence of change does not exclude organic heart disease, including narrow-

ing of the coronary arteries. The value of the anoxemia test and of the effort test is in the frequency with which changes occur in the presence of organic heart disease.

Rheumatic Heart Disease.—Four out of eight patients with mitral disease (with or without concomitant aortic disease) showed, during anoxemia, electrocardiographic changes similar to those seen in coronary disease.

Myxedema.—Recorded electrocardiographic changes are extensively discussed. During anoxemia, S-T segments and T waves showed a tendency to become lower. This was least marked when the electrocardiogram had been previously changed by the disease and most marked when the tracing had recently returned to normal under treatment. When the treatment was well in hand the electrocardiogram was no longer changed by anoxemia. Rarely were the changes associated with precordial pain.

Hyperthyroidism.—Four out of five patients showed significant changes in the S-T segments and in the T waves during anoxemia.

Diabetes.—The author believes that diabetes may, in itself, produce electrocardiographic changes which may clear up when the diabetes is treated, and that these changes are due to disordered metabolism caused by insulin deficiency. Insulin can also affect the electrocardiogram, partly through hypoglycemia and partly through some specific effect on the myocardium. Nine out of twelve diabetics showed significant electrocardiographic changes during anoxemia. The degree of these changes is determined both by the blood sugar concentration and the insulin content of the body.

Anemia.—As a rule, the electrocardiographic changes due to anemia are not very severe. They do not necessarily depend on the degree of anemia. When the hemoglobin was 40 per cent, or less, anoxemia produced changes in the S-T segments and in the T waves. When the patients had recovered from the anemia these could usually not be reproduced. In no case was induced anoxemia associated with precordial pain.

JULIUS JENSEN.

ADVENTURES IN RESPIRATION. MODES OF ASPHYXIATION AND METHODS OF RESUSCITATION: By Yandell Henderson. Baltimore, 316 pages, 1935. The Williams and Wilkins Co.

The title admirably describes the book. It is essentially a record of the author's own experiences, extending over nearly forty years, in various investigations of respiratory function. The book covers many phases, but its basic theme is the control of respiration by carbon dioxide, the manner in which this function may be disturbed, the consequences thereof, and the use of carbon dioxide in therapy.

Starting his scientific career at the turn of the century, the author first studied the phenomenon of circulatory failure, and even in these early investigations postulated the existence of a "venopressor mechanism"—a subject to which his subsequent work was to bring him back on many occasions. In 1905 appeared the papers of J. S. Haldane on the influence of carbon dioxide in the control of respiration, and at once Professor Henderson constituted himself "as an active propagandist for the Haldane doctrine." The suggestion, made in an address in 1909, that 5 per cent carbon dioxide with oxygen be used at the end of anesthesia to prevent apnea, was, however, received at the time with "devastating criticism." Two years later came the famous Pikes Peak expedition of Haldane, Henderson, Douglas, and Schneider. The relationship of carbon dioxide and oxygen in the control of respiration was then earnestly studied and discussed. In 1917, when "acidosis" was still synonymous with low "alkaline reserve," the author

again raised a protest, for he realized that at least at high altitudes the low carbon dioxide levels by no means constituted a state of acidosis.

Even before this time, Professor Henderson had begun the more practical investigations which have since come to be so much associated with his name, namely, his work with mine rescue apparatus, starting with his appointment, in 1912, as consulting physiologist in the United States Bureau of Mines; his vigorous and courageous supervision of the experiments leading to the development of the American gas mask during the war; his assistance in the establishment of adequate ventilation for the Holland Tunnel under the Hudson River (1920); his outstanding service in the development of an adequate technique for relief of carbon monoxide asphyxiation by means of carbon dioxide-oxygen inhalation with the H. H. inhalator (1922); and, more recently, his extension of the use of carbon dioxide-oxygen administration to resuscitation of the newborn, as well as to pneumonia, shock, and the postoperative apneic state.

In the presentation of his own views, Professor Henderson is protagonist rather than critic, and it is perhaps not unfair to say that in his discussion of some still controversial subjects not much attention is given to opposing views. In this category are the question of the validity of the Coryllos-Birnbaum hypothesis that bronchial obstruction is the immediate factor producing pneumonia, and the question of the effectiveness of carbon dioxide therapy in later postoperative states (subsequent to the immediate postanesthetic period). There are numerous critical references to the earlier chemical theories of acidosis and the acid-base equilibrium; and while such criticism of the early discussions of this subject is justified, there is in the book no recognition of the subsequent elaboration and completion of knowledge of this physicochemical system, descriptions of which have largely answered Professor Henderson's earlier criticisms. There are also in the book one or two errors of fact, as in the statement that "even when diabetic acidosis has reached the stage of coma, and death impends, no great amount of alkali has been lost from the body."

These are minor criticisms, so far as the book as a whole is concerned. *Adventures in Respiration* is not, and is not intended to be, a textbook, but a vivid and interesting account of the "adventures" of one who has contributed largely in the field of respiratory physiology. It shows the working of a vigorous and imaginative mind, the mind of a physiologist who boldly applied his newly learned knowledge to important practical problems in industry and medicine, and achieved remarkable success.

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**Executive Committee.*

The American Heart Journal

VOL. 18

SEPTEMBER, 1939

No. 3

Original Communications

FACTORS INFLUENCING THE AURICULAR MURMUR AND THE INTENSITY OF THE FIRST HEART SOUND

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STUDIES of cases of mitral stenosis in which there were varying degrees of heart block have clearly demonstrated that the presystolic murmur of mitral stenosis is produced by contraction of the auricle.^{1, 2, 3} More recently it has been appreciated that presystolic gallop rhythm and certain split heart sounds also result from sound waves initiated by auricular contraction.^{4, 5} The relation of the auricular contraction to the intensity of the first heart sound has been investigated by many observers.^{6, 7, 8} There has been no unanimity of opinion, however, as to the mechanism by which the auricular contraction modifies the intensity of the first sound. This study is reported for the purpose of emphasizing: (1) the effect of the degree of ventricular filling on the intensity of the sound produced by the auricular contraction; (2) the relative effect on the intensity of the first heart sound of (a) the time of auricular contraction and (b) the degree of ventricular filling.

METHOD

The Cambridge stethograph and the Hindle electrocardiograph were used to record the heart sounds and the electrocardiogram simultaneously. The stethograph consists of three main parts, namely, a large bell microphone that provides a 300 to 400 per cent amplification of sounds in the range between 75 and 550 cycles per second; a vacuum tube amplifier; and a recorder consisting of light source, camera, and galvanometer. The heart sounds were recorded from the apex with the subject in the recumbent position. Lead II was always used for the simultaneously recorded electrocardiogram.

CASE 1.—N. S., a 57-year-old, white, single seamstress, entered the hospital Nov. 4, 1938, with a history of Adams-Stokes attacks for three weeks preceding admission. There was no past history of rheumatic fever, chorea, dyspnea, or angina. In the physical examination the points of interest were confined to the cardiovascular system. The heart was not enlarged. The first sound at the apex was

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Received for publication March 1, 1939.

accentuated; there were a blowing systolic murmur of moderate intensity, and a presystolic murmur, both of which were maximal at the apex. The heart rate was 80 per minute, and the beating was regular. The blood pressure was 130/60. The peripheral vessels showed moderate thickening. The eye grounds were negative. The clinical impression was sclerosis of the coronary arteries with varying degrees of block, and inactive rheumatic heart disease with a minor degree of mitral stenosis.

While the patient was in the hospital the rhythm of the heart varied from normal to complete block. During periods of 2 to 1 heart block, in addition to

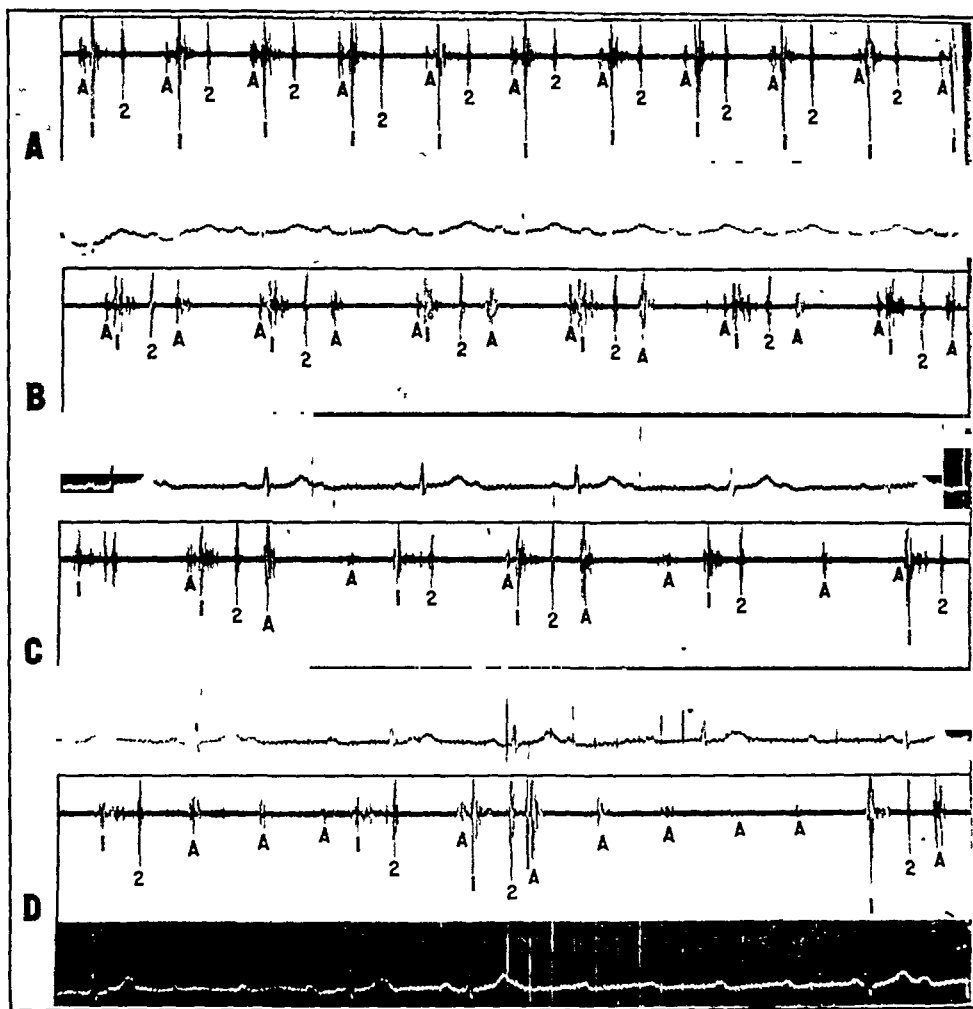


Fig. 1.—Simultaneously recorded electrocardiograms and phonocardiograms in Case 1. Bell microphone placed just inside apex. A, auricular murmur; 1, first heart sound; 2, second heart sound.

In this and the following figures, unless otherwise stated, the various tracings were taken at different times.

A, Partial heart block; B, 2 to 1 heart block; C, Complete heart block; D, Periods of ventricular standstill.

the presystolic murmur, a second murmur was audible a short time after the second heart sound. This new murmur was usually louder than the presystolic murmur, but differed from it in no other way. With 3 to 1 block two distinct murmurs were audible in addition to the presystolic murmur; the early diastolic murmur was loud, the mid-diastolic murmur faint, and the presystolic murmur barely audible. In periods of complete block, striking differences in the intensity of the first heart sound were noted in certain cardiac cycles, in addition to the

auricular murmurs of varying intensity. At the beginning of the more prolonged periods of ventricular standstill, three or four auricular murmurs, each fainter than the preceding one, were audible. During the remainder of these periods no sounds were audible, although the electrocardiogram showed that the auricles were contracting rhythmically.

Comment.—Simultaneous phonocardiographic and electrocardiographic tracings revealed several facts of interest. Fig. 1 *A* shows partial heart block with a P-R interval of 0.22 second and a rate of 80 per

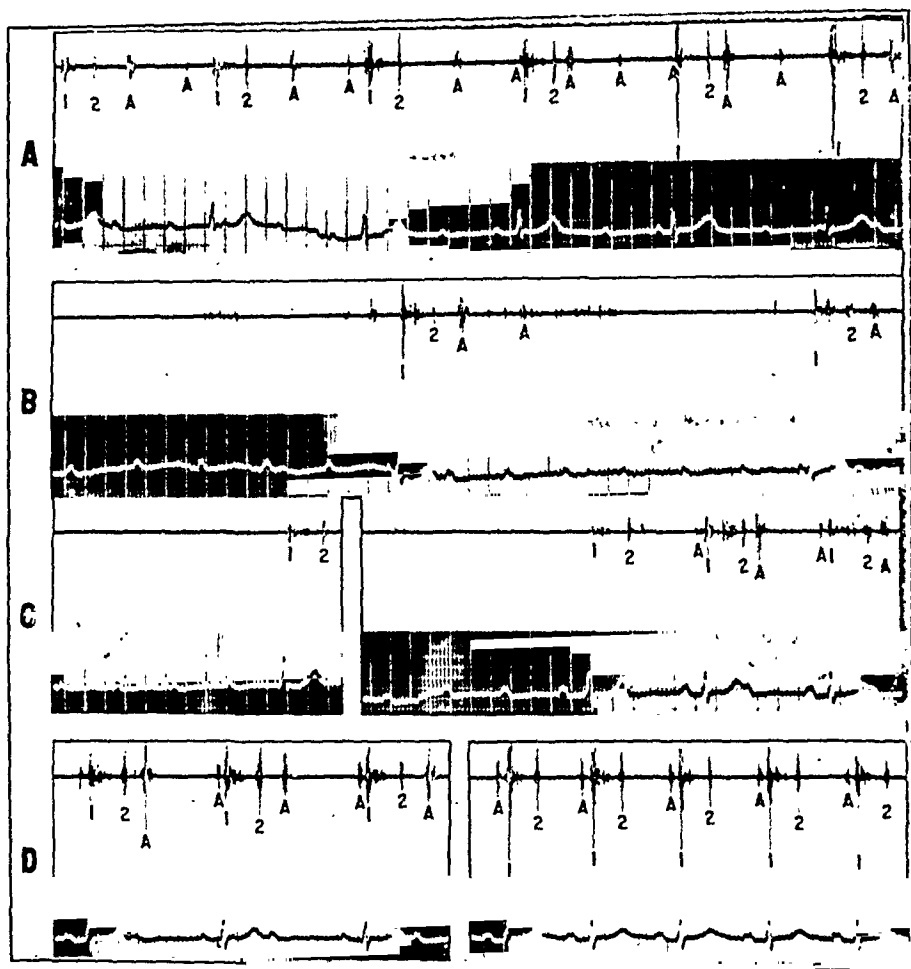


Fig. 2.—Simultaneously recorded electrocardiograms and phonocardiograms in Case 1. Bell microphone placed just inside apex.

A, Complete heart block. The first sounds in the last two beats are accentuated by the auricular contraction. *B* and *C*, Long periods of ventricular standstill. A continuous record with strips omitted between *B* and *C* and after the first ventricular beat in *C*. The first ventricular contraction in *B* and the first and second ventricular contractions in *C* follow 8-second periods of ventricular standstill. *D*, Both 2 to 1 heart block and normal rhythm. A continuous record with a few complexes omitted between the first and second portions.

minute. The presystolic murmur is readily visible. Fig. 1 *B* is a tracing of 2 to 1 heart block with an auricular rate of 84, and a ventricular rate of 42, per minute. When the auricle contracts early in diastole a murmur is produced which is louder than the presystolic murmur. Tracings *C* and *D* show complete block and periods of ventricular standstill. The

auricular rate is about 85. Again, the more closely the auricular contraction follows the second sound, the louder is the murmur produced. This is strikingly shown in the longer periods of ventricular standstill. The fifth auricular beat is barely visible on the sound tracing, and was inaudible.

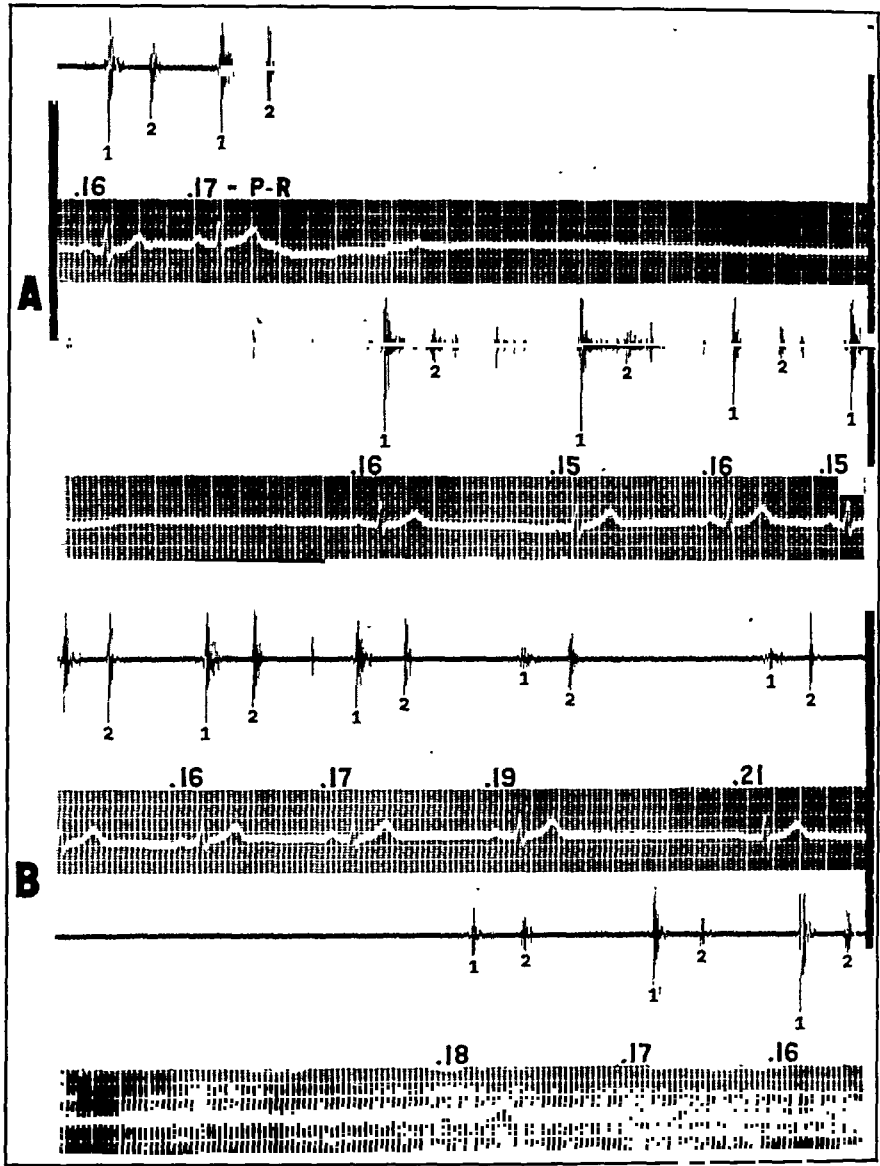


Fig. 3.—Simultaneously recorded electrocardiograms and phonocardiograms in Case 2.
A, A 5-second period of cardiac standstill without change in the P-R interval. The intensity of the first heart sound is not altered. B, Increase in P-R interval and short period of cardiac standstill. As the P-R interval is lengthened, the first heart sound decreases in intensity.

Fig. 2 A shows the effect of different P-R intervals on the intensity of the first heart sound. In this case the sound is increased in intensity with P-R intervals of 0.18 to 0.04 second. With P-R intervals outside these limits the auricular contraction has no measurable effect on the first heart sound. Tracings B and C are from the same record. In B

often so faint that it failed to reach the threshold of audibility. He gave the following explanation for this variation. When the auricular contraction immediately follows the second sound, a loud noise is produced because the blood is forced rapidly into the empty ventricle. Each succeeding auricular beat produces less sound because the engorged ventricle accepts less blood each time. Cossio¹⁰ also states that the presystolic murmur of mitral stenosis may be absent after long diastoles because of the inability of the auricle to inject blood into an overdistended ventricle.

In more recent years attention has been centered on the normal auricular sounds. These have been recorded both from the precordium and from the esophagus. Cossio and Fongi⁴ state that the auricular sound is formed by two groups of small oscillations, appearing a few hundredths of a second apart. With the receiver in the esophagus, the initial portion of the sound is more constant and predominates in the record, but when the auricular sound is recorded from the precordium, it is the second part of the sound that predominates. Wolferth and Margolies,⁶ in a study of seven cases of heart block, noticed that the murmur produced by auricular contractions falling early in diastole was louder and more prolonged than that produced by contractions late in diastole. They also concluded, as did Bramwell⁹ in his study of mitral stenosis, that the auricular murmur which they recorded was produced by the passage of blood from auricle to ventricle, rather than by the contraction of the auricular muscle itself. They based their conclusions on the time relation between the P wave in the electrocardiogram and the auricular murmur, and on the fact that the maximal auricular murmur occurred early in diastole, when the contraction would have the maximal effect on blood flow.

The tracings from Case 1 show the relation between the P wave and the auricular murmur. This murmur occurred 0.14 second after the beginning of the P wave, while the first sound started from 0.02 to 0.04 second after the beginning of the R wave. The degree of ventricular filling played the decisive role in determining the intensity of the murmur produced by the auricular contraction. As this would be true regardless of whether the auricular murmur was caused by a slight degree of mitral stenosis or by an abnormally vigorous auricular contraction, it is not possible to make an etiologic diagnosis from the tracings. The accentuated first sound with partial heart block and a ventricular rate of 80 beats per minute is, however, suggestive of mitral stenosis. During the discussion of the cause of the accentuated first sound in certain cycles during complete block, additional evidence will be presented to show that the auricular murmur in Case 1 is produced only when blood enters the ventricles, and that it is not produced by contraction of the auricular muscle itself.

First Heart Sound.—Textbooks of physiology and of physical diagnosis usually state that there are two factors in the production of the

first heart sound: (1) the sudden closing of the mitral and tricuspid valves; and (2) the contraction of the heart muscle. Dock,¹¹ in 1933, on the basis of experiments on the exposed hearts of dogs, stated that there is no muscular element in the first heart sound, and that ventricular contraction produces no audible vibrations in either empty or full hearts if tensing of the auriculoventricular valves is prevented. He stated also that if the valves are closed and the intraventricular pressure is about as high as the pressure within the auricle, ventricular contraction causes only a faint first sound; if the valves are slack and displaced toward the ventricles by the rush of blood through them, ventricular contraction produces a loud first sound. The evidence obtained in our two cases lends support to Dock's conclusions.

In Case 1 the first heart sound was intensified whenever auricular electrical systole began from 0.18 second to 0.04 second before ventricular electrical systole. This accentuation of the first heart sound by the auricular contraction has been described by many observers.^{6, 7, 8} Some authors^{6, 12} have stated that a moderate increase in intensity occurs regularly in certain cases when ventricular electrical systole precedes auricular electrical systole by a few hundredths of a second. Careful analysis of a large series of tracings obtained in Case 1 failed to reveal any accentuation of the first sound unless the P wave preceded the R wave. An explanation for this apparent discrepancy has been furnished by the work of Wolferth and Margolies¹³ on the influence of varying P-R intervals on split first heart sounds. In two cases of complete heart block the first portion of the split heart sound was not accentuated unless the P-R interval exceeded 0.03 and 0.05 second, respectively. In these cases, however, the second portion of the first heart sound was accentuated when the P wave was buried in the QRS complex. Wolferth and Margolies believed that in these cases the contractions of the right and left ventricles were not perfectly synchronized. The auricular contraction, therefore, could still influence the portion of the first sound developed from one side of the heart, although contraction of the opposite ventricle had already closed one set of valves and produced the first portion of the first heart sound.

There have been two principal explanations for the accentuation of the first heart sound by the auricular contraction: (1) It is the result of the summation of the auricular and ventricular sound waves¹⁴; (2) it is the result of a change in the position of the auriculoventricular valves at the beginning of ventricular contraction.^{6, 11} The fact that, in Case 1, accentuation of the first sound persisted when the P-R interval was shortened after long periods of ventricular standstill, and after the auricular contractions had ceased to make any sound waves, indicates that the accentuated first sound was not the summation of the normal auricular and ventricular sound waves. The best explanation of the accentuation of the first sound is that it results from an increase in intra-auricular

pressure sufficiently great to produce slackening of the auriculoventricular valves. The ventricular contraction causes sudden tightening of the previously slack valve structures and produces an intensified sound. The possibility exists that with a long P-R interval blood may flow backward, from ventricle to auricle, and produce a weak first sound because the ventricle contains less blood than normally. The fact that the auricular murmur disappears during the longer periods of ventricular standstill indicates that the ventricles are too full to accept more blood, which renders this explanation untenable. Likewise, accentuation of the first sound cannot result from an increase in the amount of blood in the ventricles brought about by the immediately preceding auricular contraction, because accentuation occurs with short P-R intervals even when the auricular contractions have ceased passing much blood into the ventricles.

Accentuation of the first heart sound occurred when the auricular murmur (not the P wave) started from 0.07 second before the beginning of the first sound to 0.07 second after the beginning of the first sound. The fact that the first sound may be accentuated, even when the auricular murmur is prevented by the ventricular contraction, indicates that the auricular pressure has already risen before the auricular murmur is produced, and that the murmur does not result from the contraction of the auricular muscle itself. The time relation suggests that the rise in intra-auricular pressure with displacement of the auriculoventricular valves toward the ventricle is the important factor in the production of the accentuated first heart sound, and that little flow of blood from auricle to ventricle is necessary to produce accentuation of the first heart sound. This is corroborated by the fact that the first sound is accentuated when the P-R interval is short and the auricular contraction is no longer passing enough blood into the ventricle to produce a murmur.

A second major factor modifying the intensity of the first heart sound is the ventricular rate. This is best shown in Fig. 2 *D*. The first portion of the tracing shows 2 to 1 block with a P-R interval of 0.2 second; the second, normal rhythm with the same P-R interval. With the more rapid rate and a shorter time for ventricular filling, the first sound is much louder than with the slower rate. The louder first sound with the more rapid rate is the result of the shorter ventricular diastole rather than of a change in the auricular beat, since the P-R intervals are the same at both rates, and since in this particular subject studies during periods of complete block have shown that the auricular contraction has no effect on the first sound when the P-R interval is as long as 0.2 second. Likewise, after prolonged periods of ventricular standstill the first sound is uniformly weak unless the auricular contraction immediately precedes it, even though, as indicated by the absence of the auricular murmur, the ventricle is still full of blood. The longer the period of ventricular diastole, the more time the auriculoventricular valves have to float back to a position of closure. Thus, when the ventricle contracts most of the

slack has already been removed from the valves and a less intense sound is produced. If contraction of the ventricular muscle played an important part in the production of the first heart sound, the sound should be intensified in 2 to 1 block, for the longer diastole and the two auricular contractions allow the ventricle to fill more completely.

Case 2 offered an opportunity to ascertain whether the auricular contraction or the ventricular rate is the predominant factor in producing a first heart sound of normal intensity. Pressure on the carotid sinus produced periods of cardiac standstill, some of which were terminated by beats with a normal P-R interval, others by beats with a prolonged P-R interval. Following periods of cardiac standstill lasting as long as 5 seconds, the first sound of the initial beat was of normal intensity when the P-R interval was unchanged; it was uniformly greatly decreased in intensity when the P-R interval was prolonged beyond 0.18 second. Thus, in both of our cases, when the P-R interval was short enough to influence the character of the first sound, prolongation of ventricular diastole had little effect on the intensity of the first sound. In Case 1, when the P-R interval was sufficiently long not to be influenced by the auricular contraction, the first sound became progressively weaker as the duration of diastole increased.

Wolferth and Margolies⁶ have made the suggestion that the duration of the auriculoventricular interval within the normal range may be of importance in determining the character of the first heart sound. Keith,¹⁵ in a study of rheumatic heart disease in children, found that the P-R interval could be predicted with a fair degree of accuracy from the intensity of the first heart sound. The observations in Case 2 indicate that under certain conditions an increase in the P-R interval may be recognized clinically if sufficient attention is paid to the intensity of the first heart sound. This point has proved to be of practical value in the diagnosis of first degree heart block.

SUMMARY AND CONCLUSIONS

1. Two subjects, one with an auricular murmur and varying degrees of heart block, the other with attacks of partial heart block and cardiac standstill induced by pressure over the carotid sinus, were studied by means of simultaneously recorded electrocardiograms and phonocardiograms.

2. The auricular murmur recorded from the precordium was not the result of sound waves produced by the contraction of the auricular muscle itself. It was produced only when blood entered the ventricle.

3. The intensity of the auricular murmur in a given case depends on the difference between the auricular and ventricular pressures at the time of the auricular contraction. Early in diastole this difference is marked and the murmur loud; in the latter portion of long diastolic pauses the difference is much less, and the murmur either faint or absent.

4. The first heart sound in Case 1 was accentuated during periods of complete block when the P-R interval ranged between 0.18 and 0.04 second. Evidence is presented to show that this accentuation was the result of displacement of the auriculoventricular valves toward the ventricle by the auricular contraction.

5. The first heart sound became progressively weaker, as ventricular diastole increased in duration, when the P-R interval was too long for the auricular contraction to affect the first sound.

6. When the P-R interval was short enough for the auricular contraction to affect the intensity of the first sound, the auricular contraction played the dominant rôle in determining the intensity, and lengthening of ventricular diastole had no effect.

7. These observations support the conclusion that in normal hearts the position of the auriculoventricular valves at the beginning of ventricular contraction is the primary factor in determining the character of the first heart sound.

8. Variation in the length of the P-R interval, within normal limits, may produce striking alterations in the intensity of the first heart sound.

The authors wish to express their sincere appreciation to Dr. Soma Weiss for his many helpful suggestions and guidance in this work, and to Miss Sophia M. Simmons for technical assistance.

REFERENCES

1. Galabin, A. L.: On the Interpretation of Cardiographic Tracings and the Evidence Which They Afford as to the Causation of the Murmurs Attendant Upon Mitral Stenosis, *Guy's Hosp. Rep.* 20: 261, 1875.
2. Cohn, A. E.: The Origin of the Presystolic Murmur, *Brit. Med. J.* 2: 1153, 1909.
3. Lewis, T.: The Time Relations of Heart Sounds and Murmurs, with Special Reference to the Acoustic Signs in Mitral Stenosis, *Heart* 4: 241, 1913.
4. Cossio, P., and Fongi, E. G.: Auricular Sound, *AM. HEART J.* 11: 723, 1936.
5. Braun-Menendez, E.: The Heart Sound in Normal and Pathological Conditions. *Lancet* 2: 761, 1938.
6. Wolferth, C. C., and Margolies, A.: The Influence of Auricular Contraction on the First Heart Sound and the Radial Pulse, *Arch. Int. Med.* 46: 1048, 1930.
7. Duchosal, P., and Bourdillon, J.: L'éclat accidentel du premier bruit du coeur dans la dissociation auriculo-ventriculaire, *Arch. d. Mal. du Coeur* 27: 232, 1934.
8. Levine, S. A.: *Clinical Heart Disease*, Philadelphia, 1937, p. 391, W. B. Saunders Co.
9. Bramwell, C.: Sounds and Murmurs Produced by Auricular Systole, *Quart. J. Med. N. S.* 4: 139, 1935.
10. Cossio, P.: Comentarios sobre los fenómenos acústicos de la estrechez mitral y de algunos ruidos de soplo, según el registro gráfico de los mismos, *Rev. argent. de cardiología* 4: 383, 1938.
11. Dock, W.: Mode of Production of the First Heart Sound, *Arch. Int. Med.* 51: 737, 1933.
12. Laubry, C., and Puddu, V.: Dissociation auriculoventriculaire à rythme rapide; Étude électro et phonocardiographique, *Arch. d. Mal. du Coeur* 29: 665, 1936.
13. Wolferth, C. C., and Margolies, A.: The Influence of Varying A₁-V₁ Intervals on Split First Heart Sounds: Its Bearing on the Cause of Split Sounds and the Mechanism of the First Sound, *J. Clin. Invest.* 14: 605, 1935.
14. Cossio, P., and Braun-Menendez, E.: Estudio fonocardiográfico del bloqueo total auriculo ventricular, *Rev. argent. de cardiología* 2: 1, 1935.
15. Keith, J. D.: Variations in the First Heart Sound and the Auriculo-Ventricular Conduction Time in Children with Rheumatic Fever, *Arch. Dis. Childhood* 12: 217, 1937.

THE EFFECT OF POSTURE ON THE FORM OF PRECORDIAL LEADS OF THE ELECTROCARDIOGRAM

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PRECORDIAL electrocardiographic leads have come into general use since Wolferth and Wood¹ first employed them in the diagnosis of acute coronary occlusion. With the introduction of the new technique, it was to be expected that the use of many different precordial derivations by different workers would lead to confusion. In order to clarify this situation, the American Heart Association has recently recommended that precordial leads be standardized.² Although the optimum location of the exploring electrodes has been widely investigated, out of which has grown a measure of standardization, very little consideration has been given to alterations that occur in precordial leads with change in the position of the patient.

Numerous observations have been made of the changes occurring in the three standard leads of the electrocardiogram when the patient assumes different positions,³⁻⁹ especially with regard to the shift of the 'electrical axis' of the heart. Chest leads have been recorded, however, in only a few of these investigations. Although Katz and Robinson¹⁰ recorded electrocardiograms, including precordial leads, with subjects in eight different positions, they discussed only the changes which occurred in the three standard leads. Sigler¹¹ made chest leads with patients in the supine, sitting, and standing positions, but his paper deals chiefly with the changes found in the three standard leads.

The observations now being reported were made in an attempt to clarify the variations that might be expected in precordial leads when the posture of the subject is changed.

METHODS

Sixteen patients were studied. Four patients (Cases 1, 2, 3, and 4) exhibited normal hearts; in Case 5 there was pneumothorax on the right side with displacement of the heart to the left; three patients (Cases 6, 7, and 8) suffered from rheumatic heart disease with mitral stenosis and insufficiency and predominant enlargement of the right ventricle, and four patients (Cases 9, 10, 11, and 12) from rheumatic lesions of both the aortic and the mitral valves but with enlargement of the left ventricle predominating; in Case 13 there were emphysema and enlargement of the right ventricle; one patient (Case 14) suffered from arteriosclerotic heart disease without cardiac enlargement; two patients (Cases 15 and 16) exhibited the syndrome of chronic constrictive pericarditis. In Cases 6, 7, 10, 11, 14, and 15, chest leads were taken both before and after therapeutic doses of digitalis had been given, in order to observe the effect of this drug on the form of the

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Received for publication March 3, 1939.

chest leads. In all, forty-one sets of chest leads were made. Two or more observations were recorded on eight of the patients. On each of the remaining eight patients only one set of records was obtained. All observations were made with the patients in a basal metabolic state.

In addition to the three standard leads, three precordial derivations were recorded. The indifferent electrode was placed in the left interscapular region.¹ In one of the three chest leads the precordial electrode was placed in the midsternal line at the level of the fourth intercostal space (Chest Lead A); in the second chest lead the electrode was placed halfway between the first point and the apex (Chest Lead B); in the third, the electrode was placed at the apex (Chest Lead C). The skin was marked, and care was exercised to apply the electrodes at the same areas when subsequent records were taken. Lead plates measuring 6 x 4.5 cm. were used for electrodes. Each chest lead was taken with the patient in each of three positions, namely, supine, sitting up in bed at an angle of 90 degrees, and lying on the left side. All records were made with the right arm wire connected to the precordial electrode, and the left arm wire to the left interscapular electrode.¹ In order, however, to promote and facilitate uniformity in discussing chest leads, the films were printed so that the direction of the complexes corresponds to that in the leads recommended by the American Heart Association.²

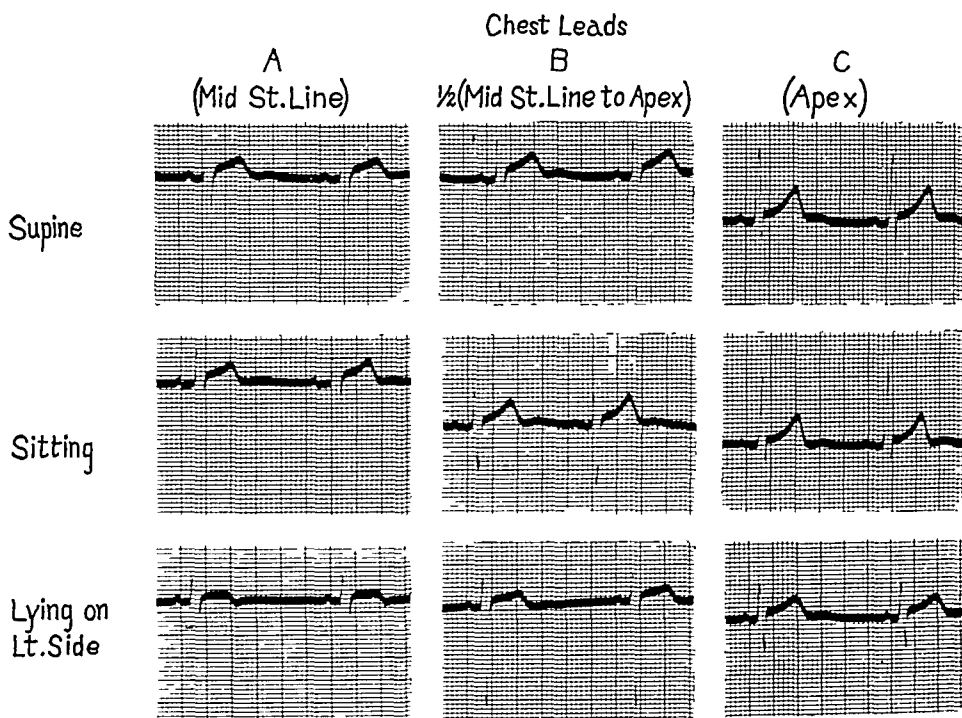


Fig. 1.—In this figure, as well as in Figs. 2 and 3, reproductions of the three chest leads (A, B, and C) are shown. Each of the leads was taken in each of three positions (supine, sitting, and lying on the left side, respectively). In Chest Lead A the exploring electrode was on the midsternal line at the level of the fourth intercostal space. In Chest Lead B the electrode was halfway between this point and the apex. In Chest Lead C the exploring electrode was at the apex. All tracings were taken with the right arm wire connected to the precordial electrode, and the left arm wire to the left interscapular electrode.¹ In order to promote and facilitate uniformity, however, the films were printed so that the direction of the complexes corresponds to that in the leads recommended by the American Heart Association.² Divisions of the ordinates equal 10^{-4} volt. Divisions of the abscissae equal 0.04 second. The electrocardiograms in all figures are reduced to half of their original size. In this figure the chest leads of E. K. (Case 1), taken April 8, 1935, are reproduced. The records in this case serve to illustrate the change that occurred in the chest leads of a normal subject as his position was changed from supine, to sitting, to lying on the left side. Decrease in the amplitude of the T waves was the most constant change, but there was also a decrease in the amplitude of the R waves. The S waves showed no constant change.

OBSERVATIONS

The results are recorded in Table I.

(1) Changes in subjects whose hearts were normal.—In these cases (Cases 1 to 4, inclusive), the most frequent change was a decrease in the amplitude of the T wave as the subject changed from the supine position to sitting, and from sitting to lying on the left side (Fig. 1). In Case 2 the T wave became diphasic in leads A and B when the subject lay on the left side, although it had been upright in the other two positions. This also occurred in lead A of the first record (April 8, 1935) taken in Case 1. The amplitude of the R wave decreased as the subject's position changed from supine, to sitting, to lying on the left side. The R and T waves varied concordantly in most instances. There was a change in the amplitude of the S wave in most cases, but it was not constant.

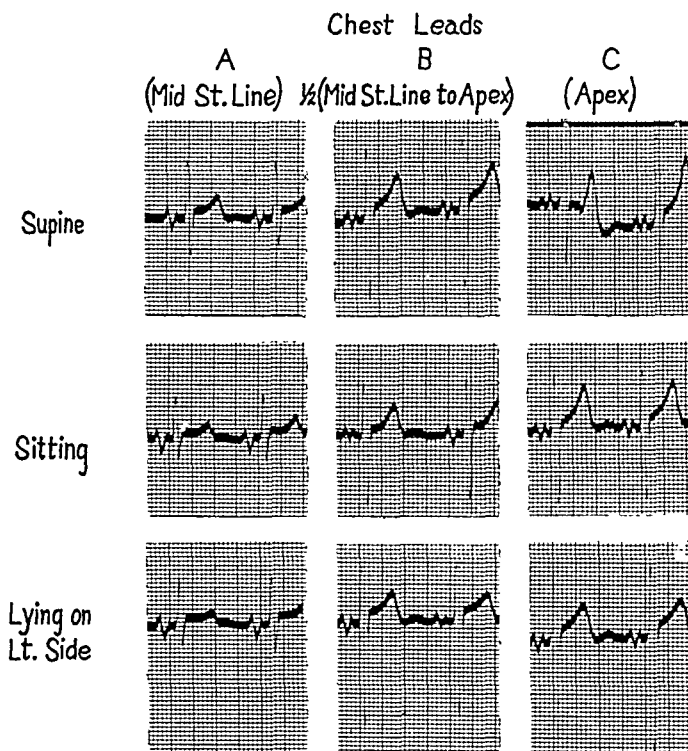


Fig. 2.—In this figure the chest leads of F. S. (Case 6), taken April 13, 1935, are reproduced. The records in this case serve to illustrate the change that occurred in the chest leads of patients exhibiting right ventricular preponderance. There was a decrease in the amplitude of the R waves and T waves as the patient's position was changed from supine, to sitting, to lying on the left side. The S waves showed no constant change.

(2) Changes in a subject with pneumothorax on the right side and displacement of the heart to the left.—In this patient (Case 5), the electrocardiogram showed no abnormal deviation of the electrical axis. Only slight changes were found in the chest leads taken in different positions. The heart was probably relatively fixed in its position as well as displaced by the pneumothorax.

(3) Changes in patients with rheumatic lesions of the mitral valve and preponderant enlargement of the right ventricle.—In these cases

TABLE
CHANGES IN THE
WITH CHANGE

CASE NO.	NAME	AGE	SEX	HOSPITAL NUMBER	DATE	AXIS DEVIATION	CHEST LEAD—A (CHEST ELECTRODE ON MIDSTERNAL LINE)								
							SUPINE			SITTING			LYING ON LEFT SIDE		
							R	S	T	R	S	T	R	S	T
1.	E. K.	24	♂	7924	4/ 8/35	0*	+	†	-	+	+	-	↓	†	±
					4/ 9/35	0	+	-	+	+	-	↓	↓	-	±
					4/10/35	0	+	-	+	↑	↓	↑	↓	↑	±
2.	H. C.	21	♂	85691	2/15/35	0	+	-	+	↑	↓	↑	↓	↑	±
3.	J. MacL.	28	♂	107863	10/ 2/35	0	+	-	+	↓	-	+	↑	↓	±
4.	J. G.	46	♂	65699	11/ 2/34	0	+	-	+	↓	↑	↓	↑	↓	±
5.	T. C.	32	♂	70382	11/23/34	0	+	-	+	+	↓	+	↑	↓	↑
					11/30/34	0	+	-	+	↓	↓	↓	↓	↑	±
					1/12/35	0	+	-	+	↓	↓	+	↓	-	±
6.	F. S.	24	♂	89187	4/13/35	R	+	-	+	↓	↑	+	↑	↓	±
					4/15/35	R	+	-	±	↑	↓	±	↓	↑	±
					4/16/35	R	+	-	±	+	↑	±	↑	↑	±
7.	A. G.	23	♂	79037	11/12/34	0	+	-	+	↑	-	↑	+	-	+
					11/14/34	0	+	-	+	↑	↑	+	↓	↓	+
					11/16/34	0	+	-	+	↓	↑	↓	↓	-	±
					11/17/34	0	+	-	+	↓	↑	↓	↑	-	±
					11/27/34	0	+	-	+	↑	↓	↑	↓	-	±
					1/10/35	0	+	-	+	↓	↑	↓	↓	↑	±
					3/28/35	0	+	-	+	+	↑	↓	↑	↑	±
8.	F. M.	32	♂	66492	11/ 1/34	0	+	-	-	↑	↓	↑	↓	↑	±
9.	H. W.	39	♂	44299	1/ 4/35	L	+	-	+	↓	↑	↓	+	↑	±
10.	E. P.	21	♂	14505	11/ 8/34	L	+	-	+	↑	↑	↑	↓	↑	±
					11/10/34	L	+	-	+	↓	-	↓	↓	-	±
					11/13/34	L	+	-	+	+	↑	↓	+	↓	+
					11/15/34	L	+	-	+	↑	↑	↓	↓	↑	±
11.	M. C.	46	♀	67280	12/10/34	L	+	-	+	↑	↓	+	↑	↑	±
					12/12/34	L	+	-	±	↓	↓	↑	↓	↑	±
					12/13/34	L	+	-	+	+	↑	+	↓	↓	±
					12/18/34	L	+	-	+	+	↓	+	↓	↑	±

*0, no axis deviation; R, right; L, left.

† + is a positive wave, - is a negative wave, ± and ± are diphasic waves.

± ↑ means wave becomes more positive, ↓ means wave becomes less positive, when no arrow is used, the wave does not change in amplitude.

I

CHEST LEAD
IN POSTURE

CHEST LEAD—B (CHEST ELECTRODE ½ WAY BETWEEN MIDSTERNAL LINE AND APEX)						CHEST LEAD—C (CHEST ELECTRODE AT APEX)						COMMENTS		
SUPINE R S T		SITTING R S T		LYING ON LEFT SIDE R S T		SUPINE R S T		SITTING R S T		LYING ON LEFT SIDE R S T				
+ - +	+↓	-↑	+↑	+ - ↓	+↓	+ - +	+ - +	+↓	-↑	+↓	+↓	-↓	+↓	On left side, Lead A, T' becomes diphasic.
+ - +	+ - ↑	+ - ↓	+↓	+ - ↓	+↓	+ - +	+↓	-↑	+ - ↓	+↓	+↓	-↓	+↓	On left side T lowest amplitude. On left side T lowest.
+ - +	+↑	-↑	+↑	+ - ↓	+↓	+ - +	+↑	-↑	+ - ↓	+↓	+↓	-↓	+↓	
+ - +	+↑	-↓	+↑	+↓	-↑	+↓	+ - +	+ - ↓	+ - ↓	+↓	+↓	-↑	+↓	On left side, Leads A and B, T' be- comes diphasic.
+ - +	+↓	-↓	+↓	+↑	-↓	+↑	+ - +	+↓	-↓	+↓	+↑	-↓	+↑	Supine T highest.
						- - +				+↓	-↑	+↓		Supine T highest.
+ - +	+↓	-↑	+ - ↓	+↓	-↑	+ - ↓	+↓	-↑	+↓	+↑	-↓	+↑		Only slight change. Sitting T lowest. Supine T highest.
+ - +	+↓	-↓	+↓	+↓	-↑	+ - ↓	+ - ↓	+↓	-↓	+↓	+↓	-↑	+ - ↓	
+ - +	+↓	-↓	+ - ↓	+↓	-↓	+ - ↓	+ - ↓	+↓	-↓	+↓	+ - ↓	-↓	+ - ↓	
+ - +	+↓	-↑	+↓	+ - ↓	+↓	+ - +	+↓	-↓	+↓	+↑	-↓	+↓		Supine T highest.
+ - +	+↓	-↑	+ - ↓	+↓	-↓	+ - ↓	+ - ↓	+↑	-↓	+↓	+↓	-↓	+↓	On left side RS-T segment elevated and T diphasic. Digitalis—1.8 gm. on 4/14/35.
+ - +	+ - ↑	+ - ↓	+↑	+ - ↓	+↓	+ - +	+↓	-↓	+ - ↓	+↓	-↓	+↓		Supine and on left side T diphasic.
+ - +	+↑	-↓	+↓	+↓	-↑	+ - ↓	+↓	-↓	+↓	+↑	-↑	+↑		Sitting and on left side RS-T seg- ment elevated.
						+ - +	+↑	-↓	+ - ↓	+↓	-↑	+↓		Sitting T highest.
						+ - +	+↑	-↑	+ - ↓	+↓	-↓	+↓		Only slight change. Digitalis—1.6 gm. on 11/13/34.
						+ - +	+↓	-↑	+↓	+ - ↓	+↓	-↓	+↓	On left side T lowest.
						+ - +	+↓	-↑	+↓	+ - ↓	+↓	-↓	+↓	On left side T lowest.
+ - +	+↑	-↓	+↑	+↓	-↓	+ - +	+↑	-↓	+↑	+↓	-↓	+↓		Only slight change.
+ - +	+↓	-↑	+↓	+↓	-↑	+ - +	+↓	-↑	+↓	+↓	-↑	+↓		Supine and sitting RS-T segment slightly elevated.
+ - +	+↓	-↓	+↓	+ - ↓	+↓	+ - +	+↑	-↑	+ - ↓	+ - ↓	+↓	-↓	+↓	RS-T segment slightly elevated throughout.
						+ - -				+ - ↓	-↑			T negative or low throughout.
+ - +	+↓	-↑	+↓	+↓	-↑	+ - +	+ - ↓	-↑	+↓	+↓	-↑	+↓		Supine T highest.
						+ - +	+↓	-↑	+↓	+↓	-↑	+↓		On left side T lowest.
						+ - +	+↓	-↓	+↓	+↓	-↑	+↓		On left side T lowest. Digitalis—1.8 gm. on 11/9/34.
						+ - +	+ - ↓	-↑	+↓	+↓	-↓	+ - ↓		Sitting T lowest. Digitalis—0.2 gm. per day.
						+ - +	+↓	-↓	+↓	+↓	-↑	+↓		On left side T lowest. Digitalis—0.2 gm. per day.
+ - +	+ - ↓	+↑	+↑	+↑	-↑	+↓	+ - +	+ - ↓	+↑	+↑	-↑	+↓		On left side T lowest.
+ - +	+↓	-↓	+↓	+↓	-↑	+ - ↓	+↓	-↓	+↓	+↓	-↑	+↓		T low throughout. Digitalis—1.8 gm. on 12/11/34.
+ - +	+ - ↑	-↓	+↑	+↑	-↓	+ - +	+↑	-↓	+↑	+ - ↓	-↑	+↓		T low throughout.
+ - +	+ - ↓	+ - ↓	+↓	+↓	-↑	+ - +	+ - ↓	+ - ↓	+↓	+↓	-↑	+↓		On left side T lowest.

CASE NO.	NAME	AGE	SEX	HOSPITAL NUMBER	DATE	AXIS DEVIATION	CHEST LEAD—A (CHEST ELECTRODE ON MIDSTERNAL LINE)								
							SUPINE			SITTING			LYING ON LEFT SIDE		
							R	S	T	R	S	T	R	S	T
12.	J. McC.	23	♂	79052	11/ 3/34	L	+	-	+	+↓	-↑	+↓	+	-	+
13.	S. L.	44	♂	74633	11/26/34	R	+	-	-	+↑	-↓	-↓	+↓	-↑	-↑
14.	C. McCA.	68	♂	14258	1/15/35	0	+	-	+	+↓	-↑	+↑	+↓	-↑	+↓
					1/17/35	0	+	-	-	+↑	-↓	-	+↑	-↑	-↑
					1/19/35	0	+	-	-	+↑	-↓	-↓	+↑	-↑	+↑
15.	W. M.	36	♂	103699	9/10/35	R	+	-	+						
					9/17/35	R	+	-	+	+↓	-↓	+	+↑	-↑	+
					9/21/35	R	+	-	+	+↓	-↓	+↓	+	-	+↓
					9/26/35	R	+	-	+	+	-	±	+↓	-↑	±
					9/30/35	R	+	-	-	+	-↓	-	+↑	-↑	-
16.	I. F.	13	♂	82012	12/11/34	L									

(Cases 6 to 8, inclusive) alterations similar to those seen in subjects whose hearts were normal occurred (Fig. 2). In most instances a decrease in the amplitude of the R and T waves took place as the subject's position was changed from supine, to sitting, to lying on the left side. In several instances an upright T wave became diphasic. In Case 6 the RS-T segment twice became elevated (second and fourth records, April 15, 1935 and April 19, 1935) when the subject lay on the left side.

(4) Changes in patients with rheumatic lesions of both the mitral and the aortic valves and predominant enlargement of the left ventricle.—In these cases (Cases 9 to 12, inclusive) the variations in amplitude of the R and T waves were similar to those seen in subjects with normal hearts, but more marked (Fig. 3). The S wave, however, in these cases of left ventricular preponderance, showed a definite tendency to decrease in amplitude with change in position from supine, to sitting, to lying on the left side. In Case 11 the second record (December 12, 1934) showed diphasic T waves in leads A and B with the patient in the supine position which became upright when he sat up or lay on the left side.

(5) Changes in a patient exhibiting emphysema and enlargement of the right ventricle.—In this patient (Case 13) the T waves were negative; the changes in the amplitude of the R and T waves were similar, however, to those which occurred in patients with rheumatic heart disease and right ventricular preponderance.

I—CONT'D

CHEST LEAD—B (CHEST ELECTRODE ½ WAY BETWEEN MIDSTERNAL LINE AND APEX)						CHEST LEAD—C (CHEST ELECTRODE AT APEX)						COMMENTS
SUPINE R S T		SITTING R S T		LYING ON LEFT SIDE R S T		SUPINE R S T		SITTING R S T		LYING ON LEFT SIDE R S T		
						+ - +				+↓ -↑ +↓		
+ - -		+↑ - -↓		+↓ - -↑		+ - -		+↑ -↓ -↓		+↓ -↑ -↑		Supine T highest.
+ - +		+↓ - +		+ -↑ +		+ - +		+↓ - +		+ -↑ +↓		Sitting T lowest.
+ - -		+↑ -↑ -↓		+↑ -↑ +↑		+ - -		+↑ -↓ -↓		+↑ -↑ +↑		Only slight change. On left side T negative or diphasic.
+ - -		+ -↓ -↓		+↑ -↑ +↑		+ - -		+ -↓ -↓		+↑ -↓ +↑		Digitalis—1.7 gm. on 1/16/35. On left side T negative or diphasic.
+ - ±						+ - -						Only slight change.
+ - ±		+ - ±↓		+↑ -↑ ±		+ - ±		+↓ -↑ ±		+↑ - ±↑		In Leads B and C, T diphasic.
+ - ±		+↑ -↓ ±↓		+ -↑ -		+ - ±		+ - ±↓		+↓ -↓ -		On left side: Lead A, T becomes diphasic; Leads B and C, T be- comes negative.
+ - ±		+ -↑ -↓		+↑ - -↓		+ - ±		+↑ - -↓		+↓ -↓ -		On left side: Lead A, T becomes diphasic; Leads B and C, T be- comes negative.
+ - -		+↓ - -↑		+↑ - -		+ - -		+↓ -↓ -↓		+↑ -↓ -		Only slight change. Digitalis—1.8 gm. on 9/28/35.
						+ - ±		+↓ -↑ ±		+↑ -↓ ±↓		On left side RS-T segment becomes slightly elevated.

(6) Changes in a patient suffering from arteriosclerotic heart disease without cardiac enlargement.—In Case 14 the T waves were negative or diphasic in the second and third records (January 17, 1935 and January 19, 1935). They were inclined to be most negative with the patient in the sitting position, and, in leads B and C, became diphasic instead of negative when the subject lay on the left side.

(7) Changes in patients suffering from chronic constrictive pericarditis.—These patients (Cases 15 and 16) showed only slight variations in the amplitude of the R, S, and T waves with change in posture. This may be attributed to the relative fixation of the heart which was shown to occur in such cases by Stewart and his associates,^{12, 13} as well as by Cushing and Feil.¹⁴ In Case 15, however, the T waves changed from positive to diphasic in lead A, and from diphasic to negative in leads B and C.

(8) Observations relating to digitalis.—In six patients (Cases 6, 7, 10, 11, 14, and 15), chest leads were taken both before and after therapeutic doses of digitalis had been given. Those taken after the administration of the drug showed the changes described by Stewart and Watson,¹⁵ but the variation in the amplitude of the R, S, and T waves in response to change in posture showed no deviation from the trend seen in the chest leads taken before the drug was given.

COMMENTS

Our observations show that the form of the chest lead varies with change in posture both in normal subjects and patients with heart disease, regardless of the size of the heart or the deviation of the electrical axis. The changes were less marked in cases of chronic constrictive pericarditis, in which the position of the heart was relatively fixed. The general trend was toward progressive decrease in the amplitude of the R and T waves as the subject's position was changed from supine, to sitting, to lying on the left side. The T waves, in some cases, became diphasic instead of positive, and negative instead of diphasic (Fig. 4).

Although the variation in amplitude of the waves of the chest leads followed certain trends, as has been pointed out, neither the amplitude nor the direction of the change could be predicted with any certainty in individual cases. Moreover, patients often showed different variations on subsequent days.

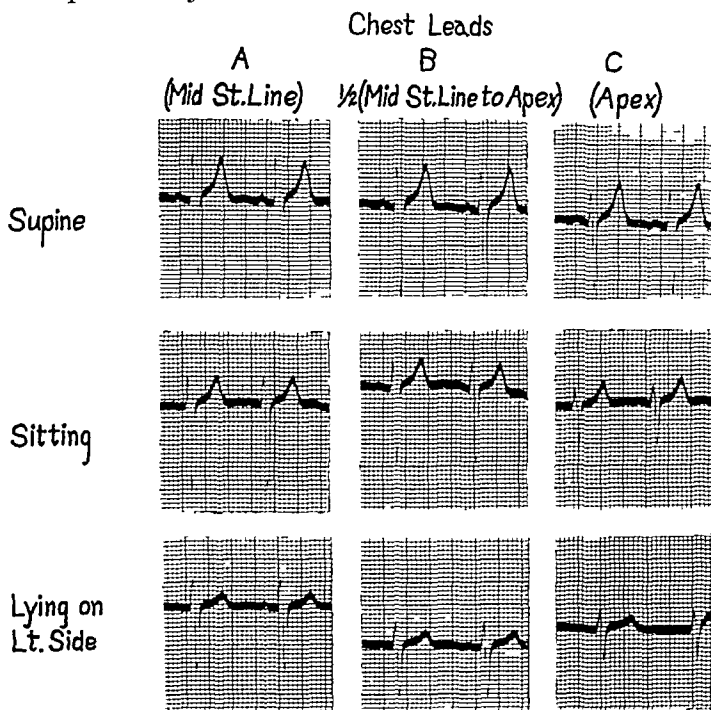


Fig. 3.—In this figure the chest leads of H. W. (Case 9), taken Jan. 4, 1935, are reproduced. The records in this case serve to illustrate the change that occurred in the chest leads of patients exhibiting left ventricular preponderance. There was a decrease in the amplitude of the R waves and T waves, and a decrease in the amplitude of the S waves, as the patient's position was changed from supine, to sitting, to lying on the left side. The change in these cases was more marked than in patients with normal hearts.

Fig. 5 shows the magnitude, frequency, and direction of change in amplitude of the waves of chest leads taken in different positions. A comparison of chest leads taken with the patient in the supine and sitting positions (upper three figures) showed that there was a tendency for the R and T waves to be lower in the leads taken in the sitting position. The S wave, however, followed no trend. A comparison of chest leads taken with the patient in the supine position and lying on the left side (middle three figures) showed a more marked

tendency for the R and T waves to be of lower amplitude in the leads taken with the patient lying on the left side. The S wave also showed a tendency to decrease in amplitude when the patient's position was changed from supine to lying on the left side. A comparison of chest leads taken with the patient in the sitting position and lying on the left side (lower three figures) showed again the tendency of the R, S, and T waves to decrease in amplitude as the patient's position was changed from sitting to lying on the left side. All of these changes were slightly more marked in Chest Lead C than they were in Chest Leads A and B.

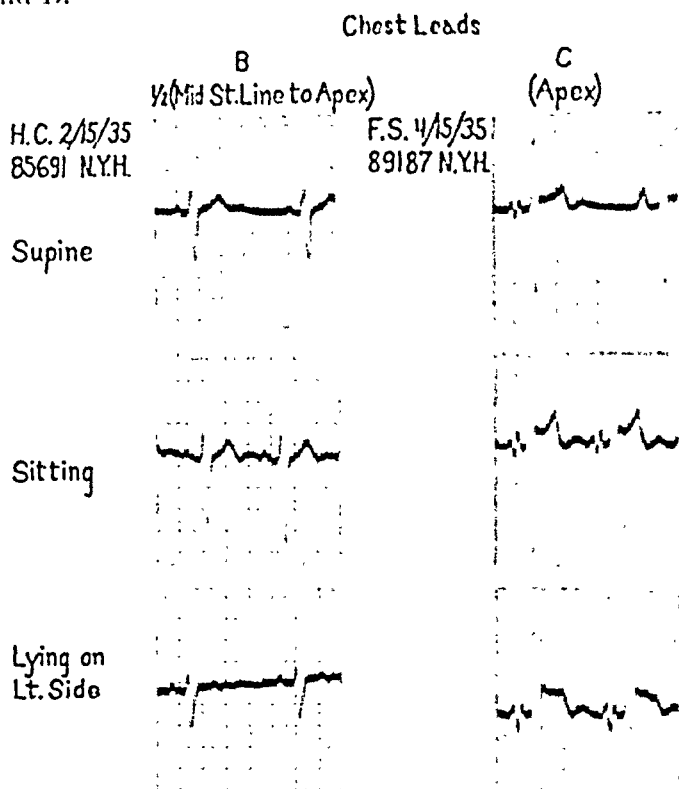


Fig. 1.—In Fig. 4B, Chest Lead B, of H. C. (Case 2), taken Feb. 15, 1935, and in Fig. 4C, Chest Lead C, of F. S. (Case 6), taken April 15, 1935, are reproduced. The records in these cases serve to illustrate the change in the form of the T waves and RS-T segments that occurred in some instances (Cases 1, 2, 6, 14, 15, and 16). The T wave may become diphasic instead of positive, or the RS-T segment may become elevated, as the patient's position is changed from supine, to sitting, to lying on the left side.

In certain instances sufficient change occurred in the form of the chest lead with change in the posture of the subject to confuse or alter the interpretation of the electrocardiogram. This was observed most frequently when the exploring electrode was placed at the apex (Chest Lead C). In the interpretation of precordial leads, the posture of the patient must be taken into account.

SUMMARY

1. Chest leads were taken with subjects in three positions: supine, sitting, and lying on the left side.

2. Three precordial leads were used. In one, the exploring electrode was placed in the midsternal line at the level of the fourth intercostal space (Chest Lead A); in the second, halfway between this point and the apex (Chest Lead B); and in the third, at the apex (Chest Lead C). In each case, the indifferent electrode was in the interscapular region.

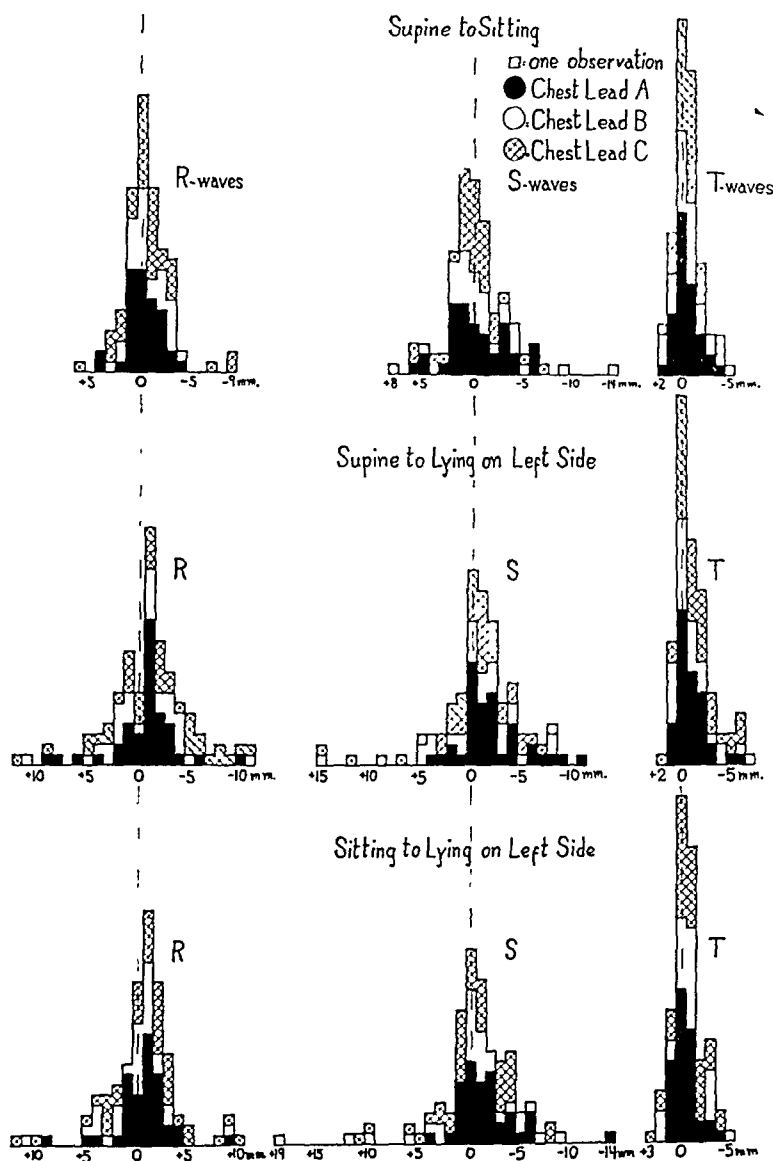


Fig. 5.—Variations in the amplitude of the R, S, and T waves of Chest Leads A, B, and C are presented in this figure as frequency diagrams. Each of the three positions (supine, sitting, and lying on the left side) is compared with each of the other two positions. The upper three figures show the variations in amplitude of the R, S, and T waves of the chest lead when the patient's position was changed from supine to sitting; the middle three figures illustrate the variations that occurred when the position was changed from supine to lying on the left side; and the lower three figures show the changes which occurred when the position was changed from sitting to lying on the left side. The solid portions of each figure are the changes that occurred in Chest Lead A, the clear portions are the changes that occurred in Chest Lead B, and the shaded portions those that occurred in Chest Lead C. Each square represents a comparison of the same wave of corresponding chest leads taken with the patient in different positions. The change in amplitude in millimeters is plotted along the abscissae, the frequency of the change, along the ordinates.

3. Forty-one observations were made on sixteen patients. The group included normal subjects and patients with heart disease. Among the latter were patients with right, and others with left, ventricular preponderance. In three patients the position of the heart was relatively fixed.

4. The variations in the form of the chest lead with change in the patient's posture are described. They consisted chiefly of a decrease in the amplitude of the R and T waves, which varied concordantly, and, in many cases, a decrease in the amplitude of the S waves, as the subject's posture was changed from supine, to sitting, to lying on the left side. In several cases positive T waves became diphasic and diphasic T waves became negative.

5. Although these changes occurred in each of the three chest leads, they were most marked in Chest Lead C (electrode at apex).

6. The changes cannot be predicted with any certainty in individual cases.

7. The importance of considering the patient's position when taking chest leads, and of taking them in the same position each time in order to make them comparable, is pointed out.

REFERENCES

1. Wolferth, C. C., and Wood, F. C.: The Electrocardiographic Diagnosis of Coronary Occlusion by the Use of Chest Leads, *Am. J. Med. Sci.* 183: 30, 1932.
2. Standardization of Precordial Leads, *AM. HEART J.* 15: 107, 1938.
3. Cohn, A. E.: An Investigation of the Relation of the Position of the Heart in the Chest to the Electrocardiogram, *Heart* 9: 311, 1921-22.
4. Cohn, A. E.: On the Relation of the Position of the Enlarged Heart to the Electrocardiogram, *Heart* 9: 331, 1922.
5. Meek, W. J., and Wilson, A.: The Effect of Change in Position of the Heart on the QRS Complexes of the Electrocardiogram, *Arch. Int. Med.* 36: 614, 1925.
6. Nathanson, M. H.: Electrocardiographic Study of Movements of the Heart with Change of Posture, *Proceed. Soc. Exp. Biol. and Med.* 28: 766, 1930-31.
7. Otto, H. L.: Effect of Altering Position of the Heart on the Voltage of the Electrocardiogram, *Proceed. Soc. Exp. Biol. and Med.* 26: 204, 1928-29.
8. Triegner, I., and Lundy, C. J.: Correlation of Shifting the Electrical Axis of the Heart with X-Ray Observation in Artificial Pneumothorax, *Am. Rev. Tuberc.* 29: 546, 1934.
9. Katz, L. N., and Ackerman, W.: The Effect of the Heart's Position on the Electrocardiographic Appearance of Ventricular Extrasystoles, *J. Clin. Invest.* 11: 1221, 1932.
10. Katz, L. N., and Robinow, M.: The Appearance of the Electrocardiogram in Relation to the Position of the Heart Within the Chest, *Am. J. Med. Sci.* 192: 556, 1936.
11. Sigler, L. H.: Electrocardiographic Changes Occurring with Alterations of Posture from Recumbent to Standing Positions, *AM. HEART J.* 15: 146, 1938.
12. Stewart, H. J., Heuer, G. J., Deitrick, J. E., Crane, N. F., Watson, R. F., and Wheeler, C. H.: Measurements of the Circulation in Constrictive Pericarditis Before and After Resection of the Pericardium, *J. Clin. Invest.* 17: 581, 1938.
13. Stewart, H. J., and Heuer, G. J.: Chronic Constrictive Pericarditis: Dynamics of the Circulation and Results of Surgical Treatment, *Arch. Int. Med.* 63: 504, 1939.
14. Cushing, E. H., and Feil, H. S.: Chronic Constrictive Pericarditis, Electrocardiographic and Clinical Studies, *Am. J. Med. Sci.* 192: 327, 1936.
15. Stewart, H. J., and Watson, R. F.: The Effect of Digitalis on the Form of the Human Electrocardiogram, with Special Reference to Changes Occurring in the Chest Lead, *AM. HEART J.* 15: 604, 1938.

INFRARED PHOTOGRAPHIC DEMONSTRATION OF THE SUPERFICIAL VENOUS PATTERN IN CONGENITAL HEART DISEASE WITH CYANOSIS*

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INFRARED photographic demonstration of the superficial veins already has acquired definite diagnostic value. The numerous prominent veins visualized in infrared photographs of patients with increased intra-abdominal pressure due to large tumors, ascites, or advanced pregnancy present an appearance different from the normal superficial venous pattern, which is usually composed of a few narrow, scattered veins. In cirrhosis of the liver the superficial venous pattern becomes more complex and prominent because of portal hypertension. This occurs in the absence of ascites, also, and is considered a satisfactory confirmatory sign.¹

PROCEDURE

All three patients reported here have congenital heart disease with cyanosis, clinically diagnosed as Fallot's tetralogy. Infrared photographic studies were made to determine whether any abnormalities of the superficial venous system could be demonstrated in this type of heart disease. Control photographs of each patient were made with panchromatic film. In addition, studies of normal individuals and of patients with compensated and decompensated rheumatic and nonrheumatic heart disease were made. One patient with *cor pulmonale* secondary to bronchiectasis was studied in a similar manner.

The infrared photographs were taken with a film-pack camera, using 6.5 x 9 cm., Eastman, infrared-sensitized plates. The lens was stopped down to f:11 after the image had been focused on the ground-glass screen. A red filter was then placed in front of the lens. Illumination was secured from four "photoflood" bulbs (500 watts each), set in aluminum reflectors and placed about 5 feet from the patient at 45-degree angles. An exposure of from 1/10 to 1/2 second was found adequate, depending on the lens aperture. The plates were developed in x-ray processing solutions in total darkness, according to the manufacturer's directions. Projection prints were made on No. 4 glossy paper.

CASE REPORTS

CASE 1.—J. B., a 7-year-old boy, complained of dyspnea on slight exertion. He had been a normal infant, and was apparently in good health until the age of 3 months. At that time cyanosis of the lips became evident, and progressed until he had a generalized dusky hue, most marked over his face. His growth had been normal. Within the preceding year there had been a rapid, progressive decrease of exercise tolerance. He was in a fair state of nutrition and of average mentality.

His heart rhythm was normal. A loud, blowing systolic murmur was heard over his entire precordium. His neck veins were not distended. Advanced clubbing of the fingers and toes, with cyanosis of the nail beds, was present.

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Received for publication Feb. 17, 1939.

Roentgenologic examination of his chest revealed a sabot-shaped heart. This was most apparent when observed fluoroscopically with the patient rotated slightly into the right anterior oblique position. The hilar vascular shadows were diminished.

An electrocardiogram showed marked right axis deviation, with slurring of the main ventricular complexes in Lead II. The auriculoventricular conduction time was 0.22 second.

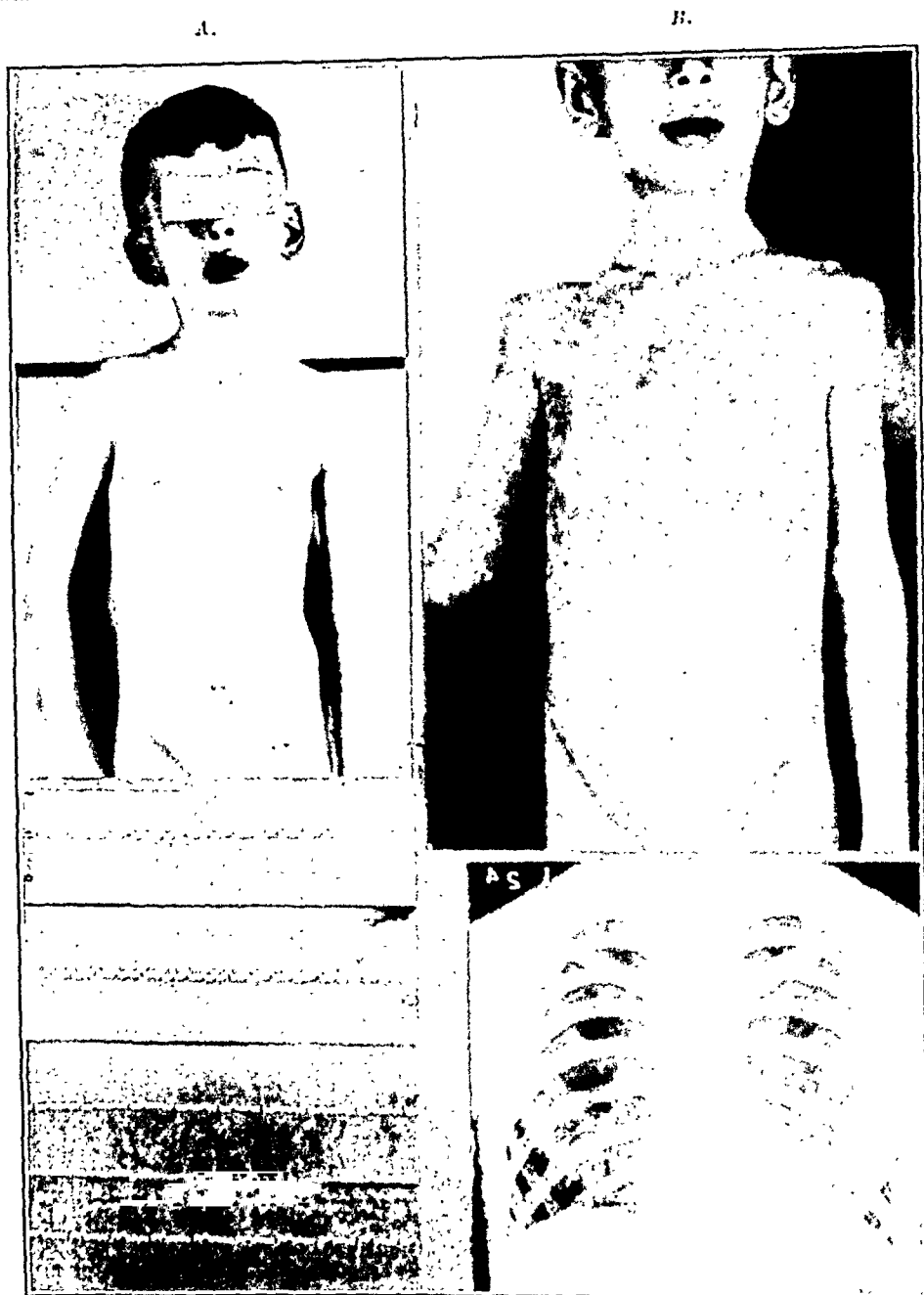


Fig. 1.—A, routine photograph on panchromatic film. B, infrared photograph, showing prominence and complexity of the superficial veins. C, electrocardiogram, showing right axis deviation. D, teleroentgenogram.

A photograph on panchromatic film showed a trace of a vein over his chest, which was seen better on direct inspection. An infrared photograph revealed re-

markable prominence and tortuosity of the entire superficial venous network. Direct inspection of the patient gave no hint as to the extent or enormous complexity of his superficial veins.

CASE 2.—H. S., a 22-year old girl who was known to have had heart disease since birth, was hospitalized because of weakness and dyspnea. Until the age of 16 she had been able to indulge in moderately strenuous exercise. At that time she developed migratory arthritis, and her activities were curtailed. Dyspnea on exertion appeared soon thereafter, and she had been confined to a bed or chair ever since. Several attacks of congestive heart failure, with enlargement and tenderness of the liver, were relieved by diuretics and digitalis. On several occasions she had had hemoptysis with chest pain, suggesting pulmonary embolism.

A.

B.



C.

D.

Fig. 2.—A, routine photograph on panchromatic film. B, infrared photograph, showing prominent superficial veins. C, teleoroentgenogram D, electrocardiogram, showing right axis deviation.

She was rather small and poorly nourished, but normally developed. Her mental abilities and interests were average. Intense cyanosis of the lips and circumoral tissues was present. The remainder of the body had a dusky tinge. Marked clubbing of the fingers and toes was present. Her heart rhythm was normal. A loud, blowing systolic murmur, most intense over the pulmonic area and to the

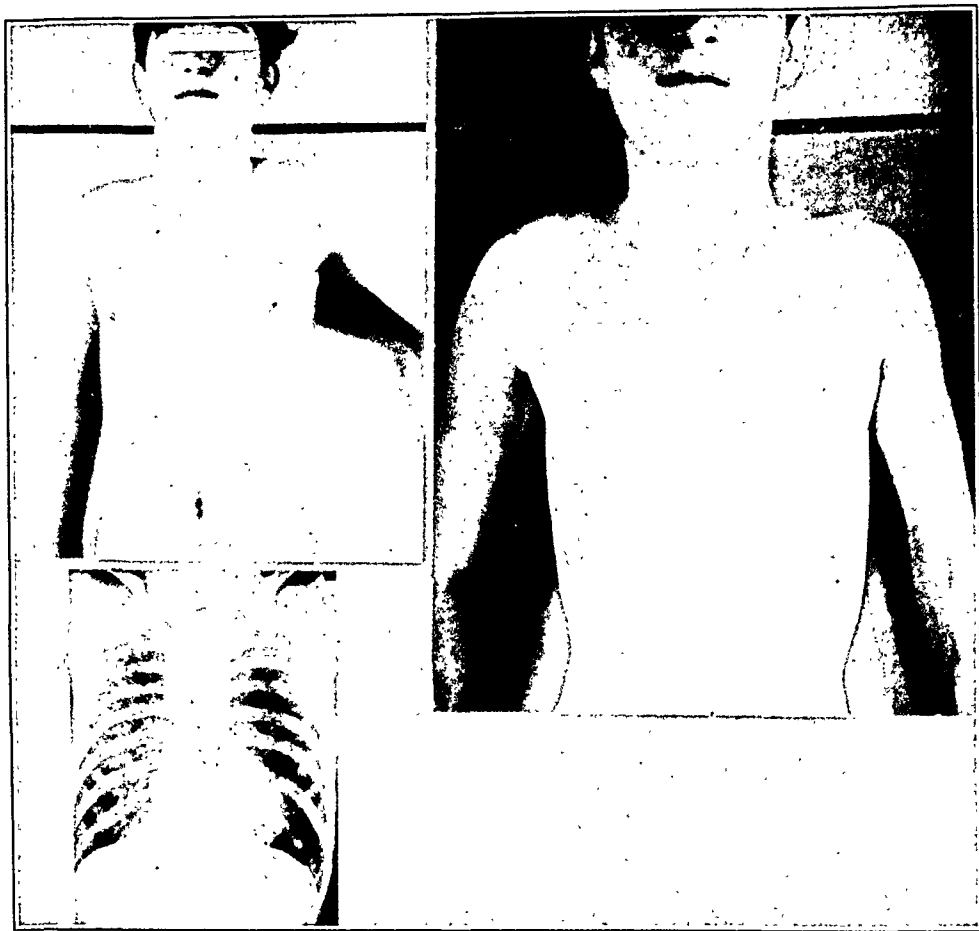
left of the sternum, was present. Her neck veins were not distended. Her blood pressure was 110/70. She had polycythemia, with 7.5 million erythrocytes and a hemoglobin of 120 per cent.

Roentgenologic examination of her chest revealed a sabot-shaped heart, the contour of which was best seen with the patient rotated slightly into the right anterior oblique position. Her electrocardiogram showed marked right axis deviation, with high P waves in Leads I and II. The main ventricular complex in Lead II was inverted. The T waves in Lead I were high and were inverted in Lead III.

She was believed to have rheumatic heart disease superimposed on the congenital cardiac malformation.

A.

B.



C.

Fig. 3.—A, routine photograph on panchromatic film. B, infrared photograph, showing prominent superficial veins. C, teleroentgenogram.

A routine photograph did not show the few veins visible over the breasts. An infrared photograph, however, showed a marked increase in the number and size of the veins over the entire area photographed. This was not as pronounced as in the first patient, possibly because of the difference in the thickness of the superficial tissues of a 22-year-old woman and a 7-year-old boy.

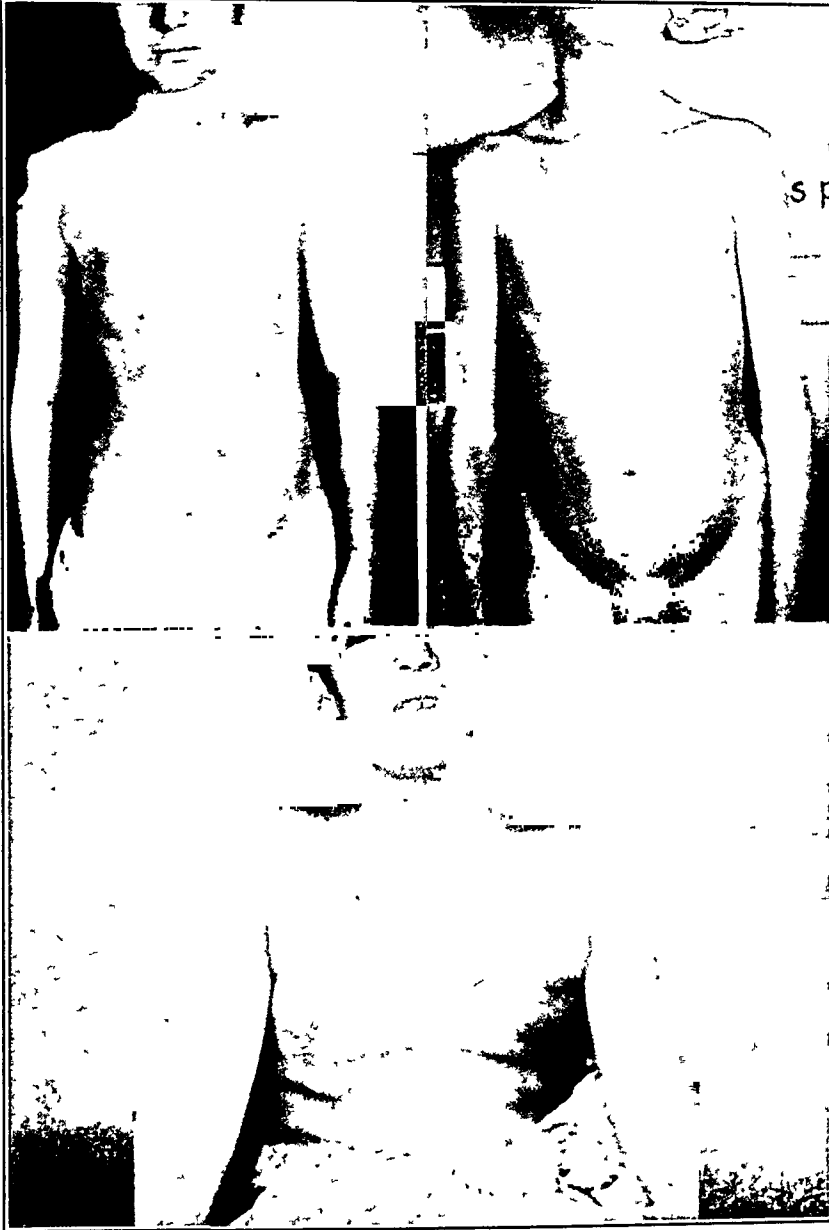
CASE 3.—H. Z., 19 years of age, had been dyspneic on slight exertion since the age of 12. Cyanosis of the lips and fingers was first seen when he was 6 months old. Clubbing of the fingers and toes appeared at the age of 3 years. The patient

could not walk until he was 6 years old because of weakness. After that time he could indulge in moderate exercise. Since the age of 11, following a fall caused by dizziness, he had been confined to bed or a chair. Edema of the ankles was noted when he was 12 years old.

The patient was frail and appeared young for his age. His mentality was considered above average. Cyanosis of the oral and circumoral tissues was marked, and the remainder of his body had a dusky appearance. A systolic murmur was audible over the entire precordium, loudest at the pulmonic area. His neck veins

A.

B.



C.

Fig. 4.—A, girl, 12 years old, with no evidence of organic heart disease. Infrared photograph shows no dilated superficial veins. B, boy, 10 years old, with rheumatic fever and mitral insufficiency. There were no evidences of congestive failure. Infrared photographs show no dilated superficial veins. C, boy, 11 years old, with active rheumatic fever and no evidences of cardiac involvement. Infrared photograph shows no dilated superficial veins.

were not unduly prominent. The blood pressure was 106/70. His liver and spleen were not palpable. Inspection of his eye grounds showed marked distention of the retinal veins. A polycythemia of 8.2 million erythrocytes, with a hemoglobin of 125 per cent, was present.

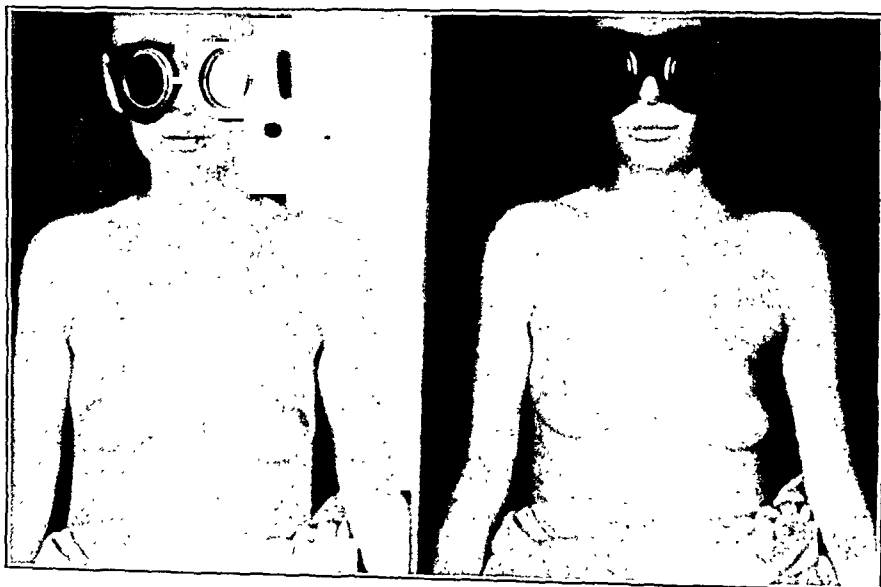
Radiographic examination of the chest and electrocardiographic study revealed abnormalities very similar to those in Cases 1 and 2.



A.

B.

Fig. 5.—A, man, 65 years old, with hypertensive and arteriosclerotic heart disease. No clinical evidences of heart failure were present when this film was taken. Photograph on panchromatic film. B, infrared photograph shows no evidences of dilated superficial veins.



A.

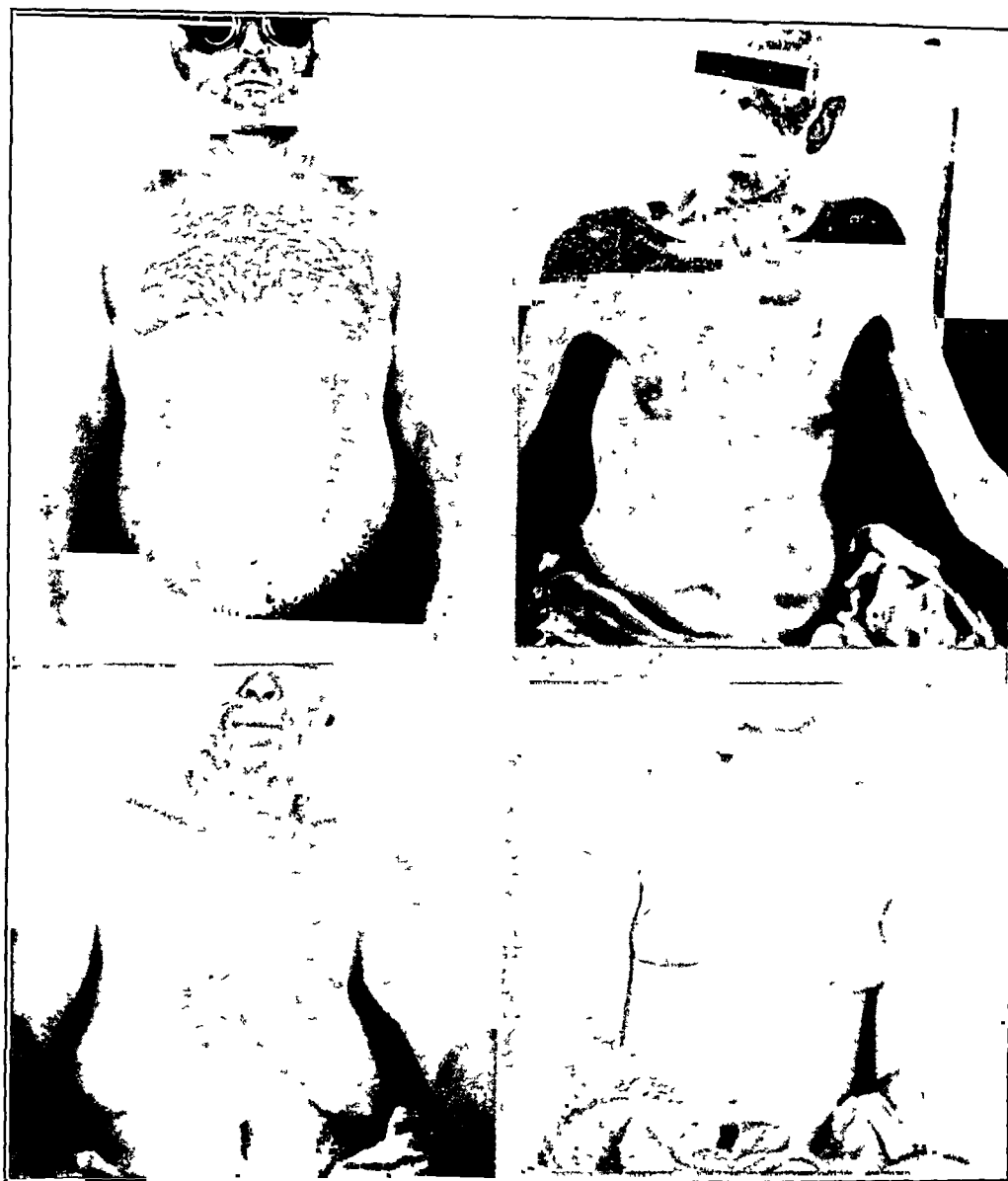
B.

Fig. 6.—A, 16-year-old girl with rheumatic fever, mitral stenosis and insufficiency, and aortic insufficiency. Had had several attacks of congestive failure, and was in failure when this photograph was taken. B, infrared photograph shows slightly dilated veins over the chest and shoulders. Note the left elbow region, with an ecchymotic area due to vein puncture.

A routine photograph of the chest did not show the single, visible, dilated vein which was present. An infrared photograph, however, revealed a marked increase in the number and size of the veins over the area photographed.

A.

B.



C.

D.

Fig. 7.—A, 40-year-old man with mitral stenosis and insufficiency and aortic insufficiency. He was ambulatory, classified as II B. Infrared photograph shows a few dilated veins over the arms. B, 64-year-old man with bronchiectasis for many years; clinical diagnosis was cor pulmonale, with right-sided heart failure. His liver was enlarged, ankle edema was present, and he was cyanotic. Electrocardiogram showed auricular fibrillation and right axis deviation. Infrared photograph shows some dilated veins over both shoulders and the left arm, but the dilatation is not marked. C, 66-year-old woman just recovering from a coronary seizure. Photograph taken day after patient had been removed from an oxygen tent. Patient still cyanotic. Electrocardiogram showed left bundle branch block. Infrared photograph, showing veins over the breasts which can also be seen on inspection. No dilated superficial veins are seen over the thorax. D, a 16-year-old girl with active rheumatic fever, mitral stenosis and insufficiency, and aortic insufficiency, in congestive failure. A minimal number of small veins visible over the upper thorax and shoulders. Infrared photograph.

COMMENT

Each of the three patients mentioned above had congenital heart disease of the Fallot's tetralogy variety. No evidences of congestive heart failure or increased venous pressure were present when the photographs were taken. Examination of the eye grounds of one patient showed marked distention of the retinal veins.

Infrared photographs visualized prominent and tortuous superficial veins in each patient. The extent of this abnormality had not been anticipated nor suspected before the infrared photographs were made.

Control studies on several normal subjects, and patients with rheumatic and hypertensive heart disease, both with and without congestive failure, did not show similar superficial venous abnormalities. It is interesting to note that the patients with decompensated organic heart disease and the patient with cor pulmonale showed an increase of moderate degree in the number and size of the veins over the shoulders and arms. This may be a reflection of the increased pressure in the right auricle.

White² states that cyanosis in "maladie bleu" is dependent on three factors: (a) the shunt of the venous blood into the systemic circulation, (b) dilatation of the skin and superficial mucous membrane capillaries, with peripheral slowing of the blood stream, and (c) insufficient oxygenation of the blood in the lungs.

The present study indicates the possibility of a fourth cause, which may be only an extension of the second reason for cyanosis advanced by White. This, as suggested by the infrared photographs, is a congenital abnormality of the superficial venous tree which may be related to the cardiac malformation.

Prominence of the superficial veins in patients with abdominal tumors is believed to be due to increased intra-abdominal pressure, and similar patterns in patients with cirrhosis of the liver are believed to be secondary to portal hypertension, with development of a collateral circulation. It is important to note that no clinical evidences of increased venous pressure were present in the patients reported here, and despite this fact the number and size of the veins were greatly increased.

SUMMARY

A marked increase in the number and size of the superficial veins was demonstrated by means of infrared photography in three patients who had congenital heart disease with cyanosis.

REFERENCES

1. Jankelson, I. R., and Baker, H.: Infra-red Photography of the Abdominal Wall in Portal Cirrhosis of the Liver, *Am. J. Digest. Dis.* 5: 414, 1938.
2. White, P. D.: *Heart Disease*, Ed. 2, page 196, 1938, Macmillan.

PLETHYSMOGRAPHIC STUDIES OF PERIPHERAL BLOOD FLOW IN MAN

III. EFFECT OF SMOKING UPON THE VASCULAR BEDS IN THE HAND, FOREARM AND FOOT*

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THE role of tobacco smoking in the production of organic changes in the cardiovascular system has been the subject of extensive laboratory and clinical research, but, as pointed out by Thienes and Butt,¹ most of the early work cannot be properly evaluated because of the lack of adequate controls. Nevertheless, it has been fairly well established that smoking does cause peripheral vasoconstriction, as indicated both by lowering of skin temperature²⁻⁵ and by plethysmographic measurements showing diminished blood flow.^{6, 7} Unfortunately, since the temperature of the skin depends for the most part upon the rate of blood flow through the superficial vessels, and since the above-mentioned plethysmographic studies were performed upon the hand, in which there are many cutaneous blood vessels capable of responding to stimuli, very little information can be derived from such work as to the effect of smoking upon the arteries and arterioles in the muscles. In view of the involvement of the latter vessels in thromboangiitis obliterans and other vascular disorders of the extremities, it was thought worthwhile to re-investigate this subject by making plethysmographic studies of the forearm, which consists principally of muscle.

METHOD

Nine normal subjects and thirteen patients‡ with various types and degrees of peripheral vascular disease were studied. Most of the subjects were tested repeatedly. With the exception of three nonsmokers (F. M., J. M., and M. M.), all were habitual smokers who had abstained for at least two hours before the test. Plethysmographic studies were generally made on two extremities simultaneously; the method employed was essentially the same as that described in previous reports.^{8, 9} In the case of the upper extremity, only the upper portion of the forearm was enclosed in the plethysmograph; the wrist and hand were immersed in water in an outer chamber. The temperature of the room was maintained between 25 and 27° C. (unless otherwise indicated), and the temperature of the water in the plethysmographs (to be designated hereafter as bath temperature)

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†Work done in part during the tenure of the Richard and Ella Hunt Sutro Fellowship.

Aided in part by the Samuel and Regina Kuhn Fund.

Received for publication March 6, 1939.

Presented before the American Physiological Society, April, 1939, Toronto.

‡A number of the patients were obtained from the Peripheral Vascular Clinic of the Mount Sinai Hospital.

was either 32° or 45° C. If reflex vasodilatation in one of the extremities in the plethysmographs was desired, the bath temperature in the other plethysmograph was raised to 45° C, a third extremity was generally immersed in water at the same temperature, and the subject was covered with blankets. Blood flow measurements were made only after reflex vasodilatation, as indicated by generalized sweating, had been present for at least fifteen minutes.

Ten to fourteen control blood flow measurements were obtained by applying a venous occlusion pressure to the limb, proximal to its insertion into the plethysmograph, and recording upon a kymograph the rate of increase in extremity volume. The subject was then permitted to smoke one or two cigarettes of a common brand; during this time (generally about six to eight minutes) and for the following half hour, blood flow measurements were made at short intervals. In the case of the forearm, a blood pressure cuff was also applied to the wrist, as advocated by Grant and Pearson,¹⁰ and a pressure of 200 mm. Hg was applied just before, and maintained during, the blood flow determination; in a number of instances, however, this cuff was left deflated for some of the records. The reason for these steps will be discussed below. During the period of smoking blood flow determinations were generally obtained at least one minute after cigarette puffs, in order to minimize the vasoconstrictor effect of the associated deep breath.

RESULTS

1. *Effect of Smoking Upon Blood Flow in the Hand.*—At a bath temperature of 32° C. (Table I, Fig. 1), all thirteen trials in normal subjects showed definite or slight reductions in blood flow either during or immediately following the period of smoking. Among the patients suffering from peripheral vascular disease (as detailed in the tables), six trials demonstrated a significant, and five a slight, decrease. In three of the latter the flow was small before smoking. In three others no response was elicited, and, similarly, in two of these the initial flow was small. In the remaining two patients in the abnormal group (F. M. and O. C.), both of whom had hypertension, there was an increase in blood flow. In the reflexly vasodilated hand (Table II, Fig. 2), smoking produced a decrease in five trials on normal subjects and no effect in another. In the abnormal group there were a decrease in two and a slight increase in one; in the latter the flow before smoking was small. At a bath temperature of 45° C. (Table III, Fig. 3), in the normal group there were a decrease in three, no effect in two, and an increase in another. In the abnormal group there were a decrease in two trials and no significant effect in one.

2. *Effect of Smoking Upon Blood Flow in the Forearm and Hand Together.*—In this group, the blood pressure cuff at the wrist was not inflated before making the blood flow measurement. Under these circumstances, as pointed out by Grant and Pearson,¹⁰ the swelling of the forearm produced by the application of the venous occlusion pressure is influenced not only by the rate of arterial flow into the part of the extremity enclosed in the plethysmograph, but also by venous return from the hand; obviously, then, changes in the caliber of the vessels in the hand will indirectly affect the rate of increase of the forearm volume.

TABLE I
EFFECT OF SMOKING UPON BLOOD FLOW AT A BATH TEMPERATURE OF 32° C.

SUBJECT	HAND			FOREARM-HAND			FOREARM			FOOT-LEG			REMARKS
	BE-FORE	DUR-ING	AFTER	BE-FORE	DUR-ING	AFTER	BE-FORE	DUR-ING	AFTER	BE-FORE	DUR-ING	AFTER	
V. B.				7.2	5.2	7.3				4.0	2.8	2.4	Normal
L. S.	16.2	16.1	15.2							3.0	1.2	2.2	Normal Room temp. 21.5° C.
	22.6	13.2	13.0							3.6	3.3	3.1	
	24.0	18.1	29.3							4.3	2.7	3.7	
	2.7	2.6	1.6	7.8	5.4	3.5	0.9	0.95	1.3	5.5	5.3	5.0	
	14.4	8.2	10.4	2.3	2.3	1.4	2.6	2.9	2.6				
A. R.	13.8	12.4	12.2	6.5	6.8	6.4	3.1	3.0	3.1				Normal
	14.8	9.7	13.1	3.5	3.3	3.3							
				5.8	8.9	6.5				3.1	2.1	2.0	
	15.1	13.5	13.0							2.0	2.1	2.3	
H. C.	13.0	5.8	9.5	10.0	5.4	6.4	3.9	4.1	3.9				Normal
	15.9	9.8	13.3	6.1	3.7	4.4	1.1	1.1	1.3				
C. R.	7.3	6.5	7.0	4.6	4.2	3.6	1.8	2.0	1.7				Normal
M. M.	12.3	6.9	13.2	3.6	3.5	4.7	1.3	1.6	1.8				Normal, nonsmoker, didn't inhale
L. C.	12.0	7.8	10.7	5.5	3.8	5.8	1.3	1.3	1.2				Normal

TABLE I—CONT'D

L. M.	12.1 3.2	6.1 3.2	6.5 2.9	9.1	6.4	5.2						4.5 2.5 4.2 3.2 4.0	4.2 2.3 4.2 2.5 3.4	3.6 2.0 3.7 2.5 3.2	Generalized arteriosclerosis
	9.2 6.9 3.9	5.9 5.3 2.0	6.0 4.2 3.5	4.2	3.7	4.7	1.5	1.8	1.8						Sympathectomized hand
L. F.	2.9 3.1	2.0 2.3	2.0									2.2 2.6	1.9 2.6	2.5	Generalized arteriosclerosis
G. M.				5.3	4.4	5.4						2.3	2.3	2.5	Hypertension
F. M.	13.2	15.0	15.0									1.4	2.1	1.7	Hypertension, nonsmoker, didn't inhale
M. B.	12.7	7.8										1.9	2.1		Terminal artery disease
A. K.	32.2	20.5										5.2	3.5		Thromboangiitis obliterans of lower extremity
S. S.	4.7		4.2												Thromboangiitis obliterans of lower extremity
J. D.	13.9		6.9									7.6		8.4	Scleroderma of upper extremity
O. C.	4.5	6.1	5.4	3.8 2.9	4.8 4.1	4.8 4.8	2.6 1.5	2.6 2.3	2.0 1.5			1.4	1.4	1.7	Hypertension
F. T.	16.9	15.1		12.6	9.9	11.3	4.7	4.8	5.2						Postural hypotension
J. M.	9.1 15.2	5.2 14.2	9.4 15.2												Syringomyelia, normal extrem. Abnormal extrem.—loss of pain and temp. sense— warmer than other

All figures represent blood flow per min. per 100 c.c. limb volume. Room temp. between 25° to 27° C. except when otherwise indicated.

TABLE II
EFFECT OF SMOKING UPON BLOOD FLOW IN A REFLEXLY DILATED EXTREMITY AT A BATH TEMPERATURE OF 32° C.

SUBJECT	HAND			FOREARM-HAND			FOREARM			FOOT-LEG			REMARKS
	BE-FORE	DUR-ING	AFTER	BE-FORE	DUR-ING	AFTER	BE-FORE	DUR-ING	AFTER	BE-FORE	DUR-ING	AFTER	
L. S.	26.8	22.6	24.8	10.9	11.1	9.3							Normal
	29.3	25.6	31.4	12.6	10.8	11.9	2.4	2.9	2.7				
	25.3	17.1	24.6							9.1	9.4	8.7	
A. R.	18.7	18.4	19.5	11.1	17.1	14.5							Normal
M. M.	27.9	22.8	23.5	5.6	4.8	5.5	0.8	1.0	1.1				Normal, nonsmoker, didn't inhale
H. C.	15.9	12.9	15.0	12.0	8.1	9.7	7.6	7.2	7.3				Normal
C. R.				5.4	6.2	6.5	1.2	1.4	1.3				Normal
L. M.	4.5	5.7	4.6	10.4	8.4	8.6							Generalized arteriosclerosis
	11.0	9.4	11.4										
L. F.	10.5	5.0	6.1							4.1	4.3	4.3	Generalized arteriosclerosis
K. M.				8.4	6.5	5.4							Hypertension
C. S.										4.6		3.5	Thromboangiitis obliterans of lower extremities

All figures represent blood flow per min. per 100 c.c. of limb volume. Room temp. 25° to 27° C.

As a result, blood flow measurements thus obtained reflect, to some extent, a combined response of the blood vessels in the hand and forearm. At a bath temperature of 32° C. (Table I, Fig. 1), in the normal group there were a decrease in eight instances, an increase in one, and no effect in three. In two of the latter there was initially a small blood flow. In the abnormal group, there were a definite decrease in flow in two instances, a slight decrease in two, and an increase in two others. The two trials in which an increase in flow was obtained were performed upon a patient with hypertension. In the reflexly vasodilated extremity (Table II, Fig. 2), with normal subjects there were a decrease in flow

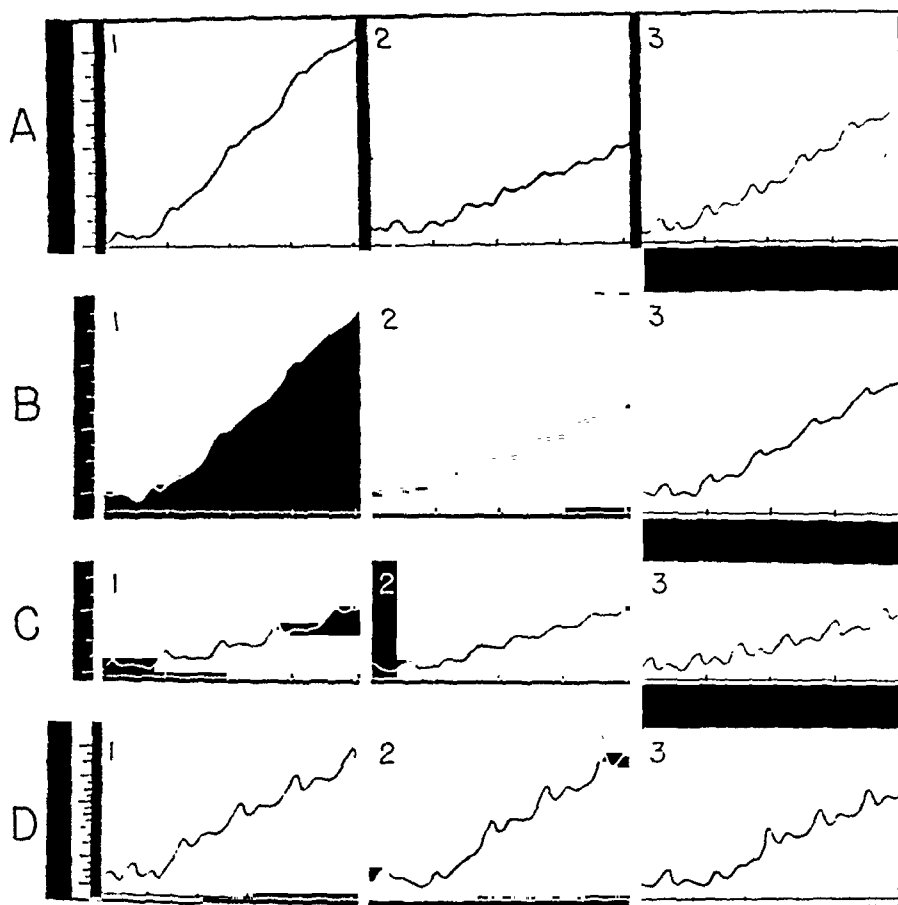


FIG. 1.—Effect of smoking upon blood flow in various blood vessel beds at a bath temperature of 32° C. A, Blood flow in hand (vol. 566 c.c.): 1, before, 5.8 c.c.; 2, during, 5.8 c.c.; 3, after, 9.5 c.c. B, Blood flow in forearm (vol. 550 c.c.) together with hand: 1, before, 10.1 c.c.; 2, during, 5.4 c.c.; 3, after, 6.4 c.c. C, Blood flow in forearm alone: 1, before, 3.9 c.c.; 2, during, 4.1 c.c.; 3, after, 3.9 c.c. D, Blood flow in foot and adjoining portion of leg (vol. 1250 c.c.): 1, before, 5.5 c.c.; 2, during, 5.3 c.c.; 3, after, 5.0 c.c. obtained in a normal subject (L.S.). All figures represent blood flow per min. per 100 c.c. of limb vol. Time in seconds. Calibrations in 0.25 c.c.

in three instances, no effect in one, and an increase in two others. In the abnormal group there was a decrease in both cases. At a bath temperature of 45° C. (Table III, Fig. 3), in the normal group there were a slight increase in two cases and a slight decrease in two others.

3. *Effect of Smoking Upon Blood Flow in the Forearm Alone.*—In this group, by means of the blood pressure cuff, a pressure of 200 mm. Hg was applied to the wrist before, and maintained during, the actual period of blood flow measurement. This permitted alterations in blood flow to be attributed to vasomotor changes in the forearm alone, for it is apparent that venous drainage from the hand could not take place under these circumstances. At a bath temperature of 32° C. (Table I, Fig. 1), in every instance (twelve trials) there was either no effect upon

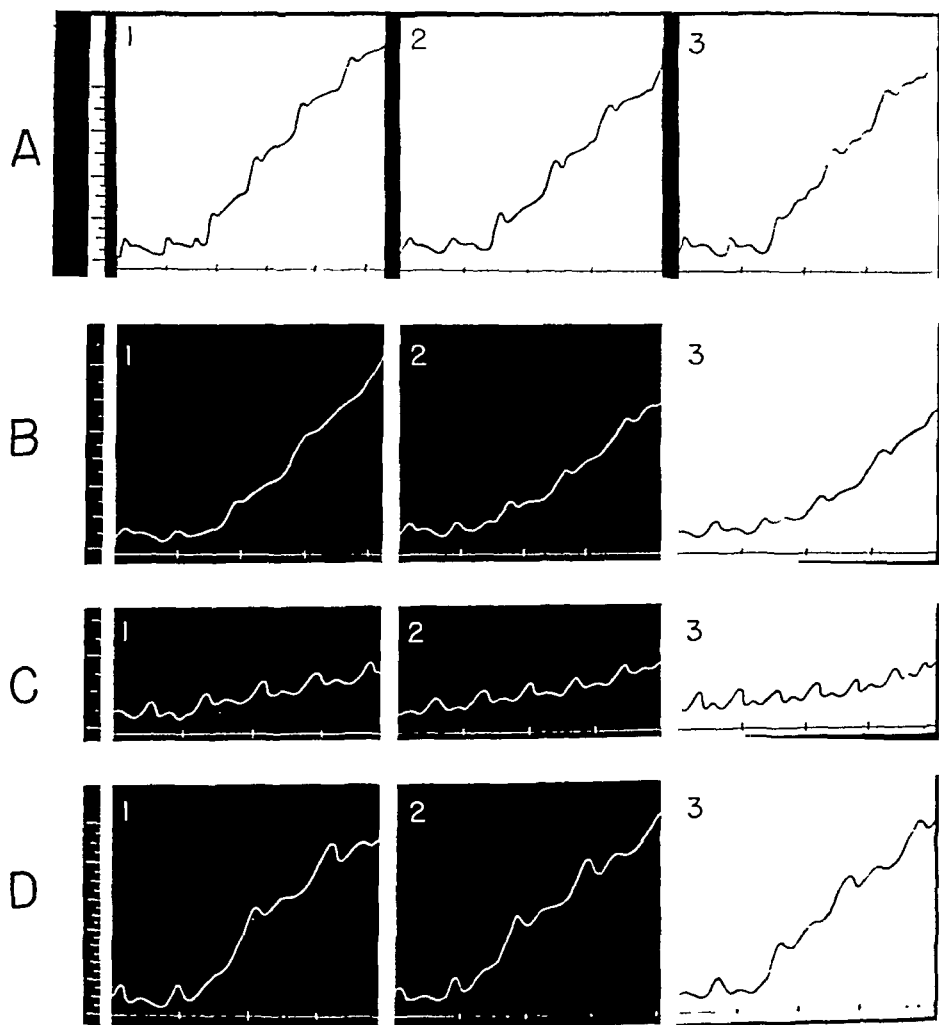


Fig. 2.—Effect of smoking upon blood flow (subject L.S.) in various blood vessel beds at a bath temperature of 32° C., but with the extremity in the plethysmograph reflexly vasodilated. *A*, Blood flow in hand (vol. 430 c.c.): 1, before, 26.8 c.c.; 2, during, 22.6 c.c.; 3, after, 24.8 c.c. *B*, Blood flow in forearm (vol. 475 c.c.) together with hand: 1, before, 12.6 c.c.; 2, during, 10.8 c.c.; 3, after, 12.6 c.c. *C*, Blood flow in forearm alone: 1, before, 2.4 c.c.; 2, during, 2.9 c.c.; 3, after, 2.7 c.c. *D*, Blood flow in foot and adjoining portion of leg (vol. 1250 c.c.): 1, before, 9.1 c.c.; 2, during, 9.4 c.c.; 3, after, 8.7 c.c.

blood flow, or even a slight increase, despite the fact that measurements of flow in the hand alone, or in the forearm plus the hand, obtained during the same procedure, showed definite and significant decreases. Likewise, in the reflexly vasodilated extremity (Table II, Fig. 2), in all cases (four trials) there was no significant decrease in blood flow with

TABLE III
 EFFECT OF SMOKING UPON BLOOD FLOW AT A BATH TEMPERATURE OF 45° C.

SUBJECT	HAND			FOREARM-HAND			FOREARM			FOOT-LEG			REMARKS
	BE- FORE	DUR- ING	AFTER	BE- FORE	DUR- ING	AFTER	BE- FORE	DUR- ING	AFTER	BE- FORE	DUR- ING	AFTER	
L. S.										12.6	12.9	11.7	Normal
										25.5	25.0	22.0	
										18.3	16.4	16.4	
	29.4	30.6	30.5	28.8	29.2	26.8				13.6	15.7	17.6	
B. L.	34.4	22.7	36.6										Normal
J. M.	37.6	38.7	38.0							9.8	10.1	9.3	Normal, nonsmoker, didn't inhale
A. R.										9.7	9.7	9.0	Normal
										11.3	9.3	8.7	
M. M.	36.2	32.0		10.6	10.7	9.8		6.4	6.8				Normal, nonsmoker, didn't inhale
H. C.	30.8	29.0	28.4	9.5	11.1	11.1		8.6	7.8				Normal
C. R.	19.8	19.8	22.7										Normal
L. M.										8.9	8.0	8.9	Generalized arteriosclerosis
										8.4	10.2	7.7	
										7.6	7.6	7.9	
L. F.	40.8	39.4								9.2	10.3	9.1	Generalized arteriosclerosis
H. M.										13.1	14.5	13.9	Hypertension
A. K.	36.6		33.2							7.9		9.6	Thromboangitis obliterans of lower extremities
C. S.	43.9	37.6											Thromboangitis obliterans of lower extremities
O. C.										6.8	7.1	6.5	Hypertension

All figures represent blood flow per min. per 100 c.c. of limb volume. Room temp. 25° to 27° C.

smoking. At a bath temperature of 45° C. (Table III, Fig. 3), a slight increase in flow was observed in one instance and no significant change in two others.

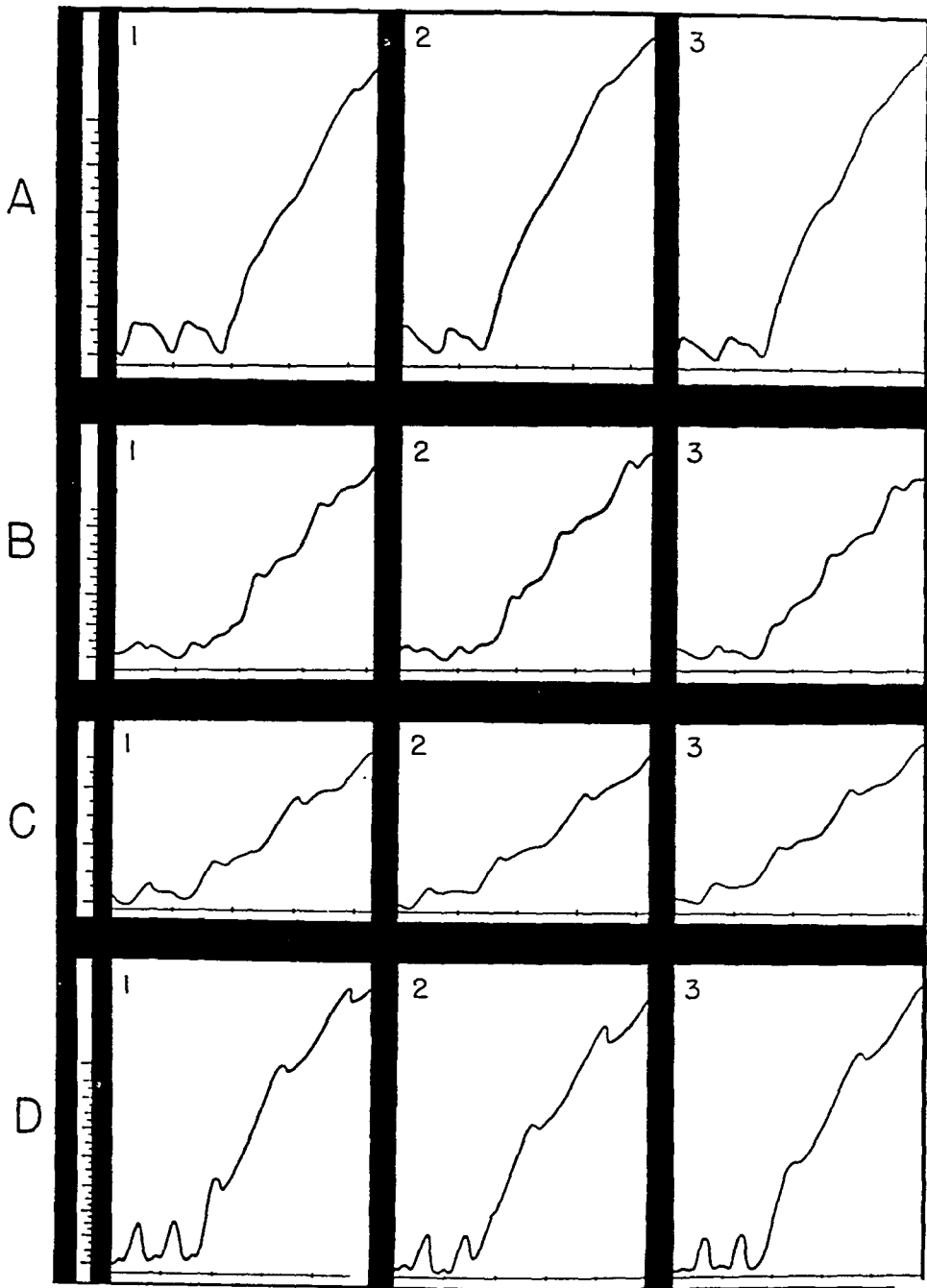


Fig. 3.—Effect of smoking upon blood flow (subject L.S.) in various blood vessel beds at a bath temperature of 45° C. *A*, Blood flow in hand (vol. 456 c.c.): 1, before, 29.4 c.c.; 2, during, 30.6 c.c.; 3, after, 30.5 c.c. *B*, Blood flow in forearm (vol. 530 c.c.) together with hand: 1, before, 28.8 c.c.; 2, during, 29.2 c.c.; 3, after, 26.8 c.c. *C*, Blood flow in forearm (vol. 500 c.c.) alone: 1, before, 10.4 c.c.; 2, during, 9.6 c.c.; 3, after, 9.6 c.c. *D*, Blood flow in foot and adjoining portion of leg (vol. 1380 c.c.): 1, before, 12.6 c.c.; 2, during, 12.9 c.c.; 3, after, 11.7 c.c.

4. *Effect of Smoking Upon Blood Flow in the Foot and Leg.*—In respect to the lower extremity, the foot and at least five inches of the

adjoining portion of the leg were within the plethysmograph, so that blood flow measurements reflected the combined response of the blood vessels in both sites. At a bath temperature of 32° C. (Table I, Fig. 1), in the group of normal subjects a definite decrease was obtained in three instances and a slight effect in one. In the remaining three trials no significant change was observed. In the group of abnormal subjects a slight decrease occurred in four, no effect in seven, and an increase in two. The increase in flow was observed in a patient with hypertension and in one with scleroderma. In the reflexly vasodilated extremity (Table II, Fig. 2) there was no significant change in blood flow (three trials) in either normal or abnormal subjects. At a bath temperature of 45° C. (Table III, Fig. 3), in the normal group there were a definite decrease in four subjects, no effect in two, and an increase in another. In the abnormal group there were no effect in two, an increase in four, and a slight decrease in one.

DISCUSSION

It is obvious from an examination of the above data that smoking produced no reduction in total blood flow in the forearm alone under any of the conditions maintained during the experiments. That this was not due to a lack of response on the part of the subject is readily proved by the fact that there was a simultaneous and significant decrease, both in the hand alone and in the forearm and the hand together, at a bath temperature of 32° C. (Table I). On the basis of the observations of Grant and Pearson¹⁰ that skin and subcutaneous tissue form about 50 per cent of the volume of the fingers, and that muscle makes up about 85 per cent of the volume of the forearm, it may be assumed that local blood flow changes in the hand are dependent to a considerable degree upon alterations in the caliber of cutaneous blood vessels, whereas in the forearm the muscle vessels play the predominant role. If these assumptions are correct, and, further, if the muscle of the forearm can be considered representative of similar tissue elsewhere at the periphery (and there is no evidence to the contrary), then the more general statement can tentatively be made that smoking causes constriction of the arteries in the skin, but apparently has little, if any, effect upon those in voluntary muscle. All of the data appear to support such a view. For instance, when vascular changes in the hand were permitted to influence the blood flow measurements obtained from the forearm (i.e., by allowing the blood pressure cuff at the wrist to remain deflated during a forearm blood flow measurement), smoking caused a decrease in flow which disappeared upon inflation of the cuff. In accord with this is the observation that in no instance was the degree of change in the forearm and hand together as great as that in the hand alone. In the studies on the lower extremity, the effect of smoking, at a bath temperature of 32° C., was much less marked than in the hand

under similar conditions; this can be correlated with the fact that a portion of leg, made up principally of muscle, was enclosed in the plethysmograph.

Another point which must be considered is the fact that blood flow through the forearm is to some extent influenced by the state of the blood vessels in the skin, which makes up about 9 per cent of the extremity volume.¹⁰ If we assume that these vessels react in the same way as similarly located arterioles in the hand,* then smoking should constrict them, causing a decrease in the rate of total blood flow. However, since the blood flow in the forearm was not only not diminished, but in some cases even increased slightly, the possibility exists that although some constriction of the blood vessels in the skin may have taken place, it was largely masked by a simultaneous dilatation of the vessels in the muscle. This view is in accord with the observations of other workers that the blood vessels in the muscle and those in the skin respond differently to various stimuli. For instance, Friedlander and her associates,¹¹ by means of thermocouples, were able to demonstrate that, with such procedures as the production of reflex vasodilatation, paravertebral block, and spinal anesthesia, the skin temperature in human subjects rose significantly while that of the muscle remained unaffected. Further, Grant and Pearson¹⁰ have shown that, in the forearm and leg, minute doses of epinephrine, introduced intravenously or subcutaneously, caused an increase in limb volume and blood flow, while in the digits definite vasoconstriction was produced. Abramson and Ferris¹² have found that with such a stimulus as a pinch, or the performance of a mental task, there was a definite decrease in blood flow in the hand, but no change, or even an increase, in flow through the forearm.

Comparison of the effects of smoking upon blood flow in an extremity under different environmental conditions reveals certain variations in the degree of response elicited. For instance, in the hand, at a bath temperature of 32° C. (equal to average skin temperature), vasoconstriction was generally produced by smoking; with reflex vasodilatation a decreased flow still resulted, but to a relatively small degree. On exposing the hand to a bath temperature of 45° C., smoking generally produced no effect, although in occasional instances a definite vasoconstriction was still observed. The same type of variation with changes in bath temperature was observed in the foot and leg, and in the forearm and hand together. As has been stressed before, smoking produced no decrease in blood flow in the forearm alone, irrespective of the state of the blood vessels.

It would appear from the foregoing that when the blood vessels in the hand are dilated, either reflexly or by the direct application of heat,

*A possible objection to this statement is the fact that there are many arteriovenous shunts in the skin of the fingers which are not present in the skin of the forearm. This anatomic finding may in part explain the differences in response of the forearm and hand.¹⁰

in blood flow. In the foot and adjoining portion of the leg the changes were in each instance relatively less marked than in the hand. In the forearm, which contains muscle to the extent of 85 per cent of its volume, there was no change in blood flow under any of the experimental conditions.

CONCLUSIONS

Judging from our results, the usual statement that smoking causes a decrease in peripheral blood flow^{1, 5, 7} should be modified to indicate that the decrease probably takes place only in the blood vessels of the skin, and not in those of voluntary muscle. It follows, therefore, that the constrictor response to smoking observed in skin vessels of the hand cannot be considered as typical of reactions of blood vessels elsewhere in the body.

We wish to express our appreciation to Mr. Joseph Marrus, Mrs. Robert Senior, and Dr. Meyer Margolis for technical assistance in carrying out the experiments.

REFERENCES

1. Thienes, C. H., and Butt, E. M.: Chronic Circulatory Effects of Tobacco and Nicotine, *Am. J. Med. Sci.* 195: 522, 1938.
2. Maddock, W. G., and Coller, F. A.: Peripheral Vasoconstriction by Tobacco and Its Relation to Thrombo-angiitis Obliterans, *Ann. Surg.* 98: 70, 1933.
3. Maddock, W. G., Malcolm, R. L., and Coller, F. A.: Thromboangiitis Obliterans and Tobacco, *AM. HEART J.* 12: 46, 1936.
4. Wright, I. A., and Moffat, D.: Effect of Tobacco on the Peripheral Vascular System, *J. A. M. A.* 103: 318, 1934.
5. Johnson, H. J., and Short, J.: The Effect of Tobacco on Skin Temperature, *J. Lab. and Clin. Med.* 19: 962, 1934.
6. Ralli, E. P., and Oppenheimer, B. S.: Changes in the Peripheral Circulation Accompanying Tobacco Angina, *Proc. Soc. Exp. Biol. and Med.* 24: 9, 1928.
7. Lampson, R. S.: A Quantitative Study of the Vasoconstriction Induced by Smoking, *J. A. M. A.* 104: 1963, 1935.
8. Abramson, D. I., Zazeela, H., and Marrus, J.: Plethysmographic Studies of Peripheral Blood Flow in Man. I. Criteria for Obtaining Accurate Plethysmographic Data, *AM. HEART J.* 17: 194, 1939.
9. Abramson, D. I., Zazeela, H., and Marrus, J.: Plethysmographic Studies of Peripheral Blood Flow in Man. II. Physiologic Factors Affecting Resting Blood Flow in the Extremities, *AM. HEART J.* 17: 206, 1939.
10. Grant, R. T., and Pearson, R. S. B.: The Blood Circulation in the Human Limb; Observations on the Differences Between the Proximal and Distal Parts and Remarks on the Regulation of Body Temperature, *Clin. Sci.* 3: 119, 1938.
11. Friedlander, M., Silbert, S., Bierman, W., and Laskey, N.: Differences in Temperature of Skin and Muscles of the Lower Extremities Following Various Procedures, *Proc. Soc. Exp. Biol. and Med.* 38: 150, 1938.
12. Abramson, D. I., and Ferris, E. B., Jr.: Unpublished observations.

HEART SOUNDS IN YOUNG ADULTS*

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HEART sounds have been recorded by various methods for many years. Although a great deal of information has been obtained by means of the older methods, at times the graphs have presented very difficult problems in interpretation. Lockhart¹ has discussed the outstanding contributions of the earlier methods and has presented a new method which overcomes many of the previous difficulties. His apparatus, called the stethograph, was used in our study.

Before records can be fully interpreted, normal standards need to be established. Reports in the literature have been meager, as far as the stethograph is concerned. Martínez Cañas^{2, 3} reported on the use of this method, but the number of normal records studied in his series was small. Horine⁴ described the clinical use of the stethograph and published records taken with this instrument. McKee^{5, 6} has reported on the heart sounds in normal children and children with rheumatic heart disease. In 90 per cent of her series of 105 normal children she found systolic vibrations which she called murmurs, but she did not regard them as significant.

Our study of the stethograms of 110 medical students was undertaken to determine the characteristics and time relationships of the heart sounds of normal young adults, and the significance of systolic and diastolic vibrations, exclusive of the heart sounds themselves, occurring in the absence of audible murmurs.

PROCEDURE

In order to eliminate extraneous sounds, the stethograms were made in a warm, quiet room, with the subject relaxed and respiration suspended. The recordings were made from the apex area with the patient reclining comfortably in the left lateral position. A microphone bell with an opening 5 cm. in diameter was carefully applied in the correct position, as determined by auscultation, and held with a rubber strap.

One of the standard electrocardiographic leads was recorded simultaneously on the same recording paper. The camera speed was routinely 50 mm. per second, which was found satisfactory, although occasional graphs were recorded at 100 mm. per second.

All of the students studied were apparently in good health; they had had physical examinations in the student health department and the majority had also had roentgenograms of the chest at the time of the physical examination. A careful search for the potential etiologic factors of heart disease was made in all cases, and no student with such a factor, or with objective signs of organic heart disease, was included in the series. Thus the subjects studied were free from organic

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Received for publication March 17, 1939.

heart disease, as judged by the criteria of the New York Heart Association. Body habitus, height, and weight were noted. The ages ranged between 20 and 30 years in 105 cases; five of the subjects were between 30 and 35 years of age.

All records were carefully analyzed, and artifacts ruled out. If necessary, the stethogram was repeated. The number of vibrations in each heart sound and the systolic and diastolic vibrations which were separate from the true heart sounds were counted in all records. When vibrations varied from heart cycle to heart cycle, an average was taken.

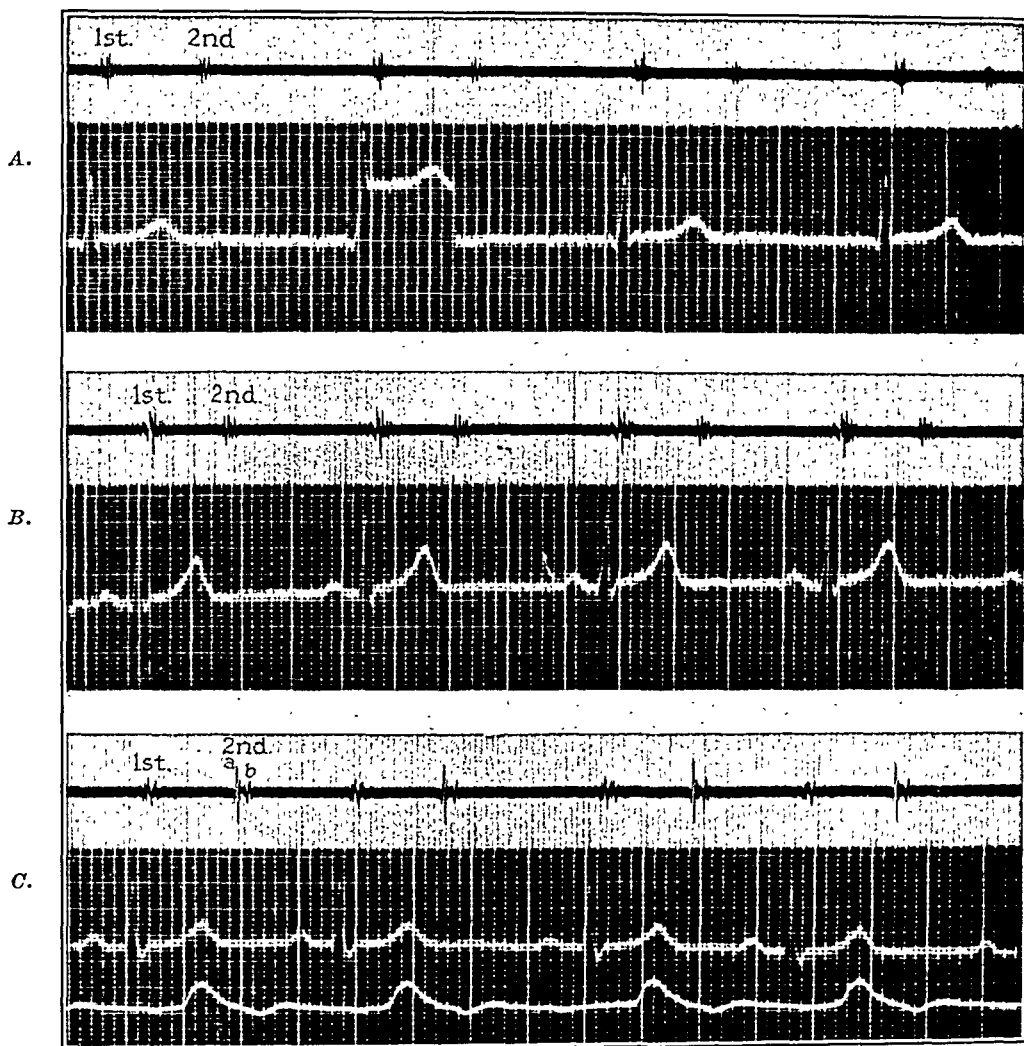


Fig. 1.—Stethograms, with Lead II of the electrocardiogram, showing: *A*, Normal heart sounds. *B*, Normal heart sounds with slight systolic vibration. *C*, Variation of normal sounds, with accentuation and reduplication of the second sound (*a-b*). Electrocardiogram and brachial pulse tracing recorded simultaneously.

RESULTS

All records examined revealed a normal sinus rhythm, with the heart rate varying from 60 to 90 beats per minute.

The first heart sound appeared within 0.04 to 0.06 second after the Q wave, or the first of the initial deflexions of the electrocardiogram. It was composed of 6 to 8 large vibrations in 86.3 per cent of the cases, and of 4 to 10 vibrations in a few isolated instances. The duration of this sound varied from 0.08 to 0.12 second.

The second sound appeared within 0.34 to 0.40 second after the Q wave. It was composed of 4 to 6 vibrations, and its duration was 0.04 to 0.06 second.

The third heart sound was recorded in 33.3 per cent of our series. It occurred 0.48 to 0.52 second after the Q wave, and 0.12 to 0.16 second after the beginning of the second sound. This sound usually had one or two vibrations of rather low amplitude.

The fourth sound was recorded in some instances, but was not constantly present or clearly distinguishable in most of the records examined (Fig. 1).

Sixty-eight records (61.8 per cent) showed vibrations during systole. These varied in number from 4 to 26. Systolic murmurs were audible in ten instances (9 per cent), and examination of the stethograms of these subjects revealed that from 16 to 26 systolic vibrations were present in every record. In the other fifty-eight cases in which there were systolic vibrations and no audible murmur, only twelve records resembled those obtained from the subjects with audible systolic murmurs, i.e., showed 16 to 26 vibrations in systole (Fig. 2).

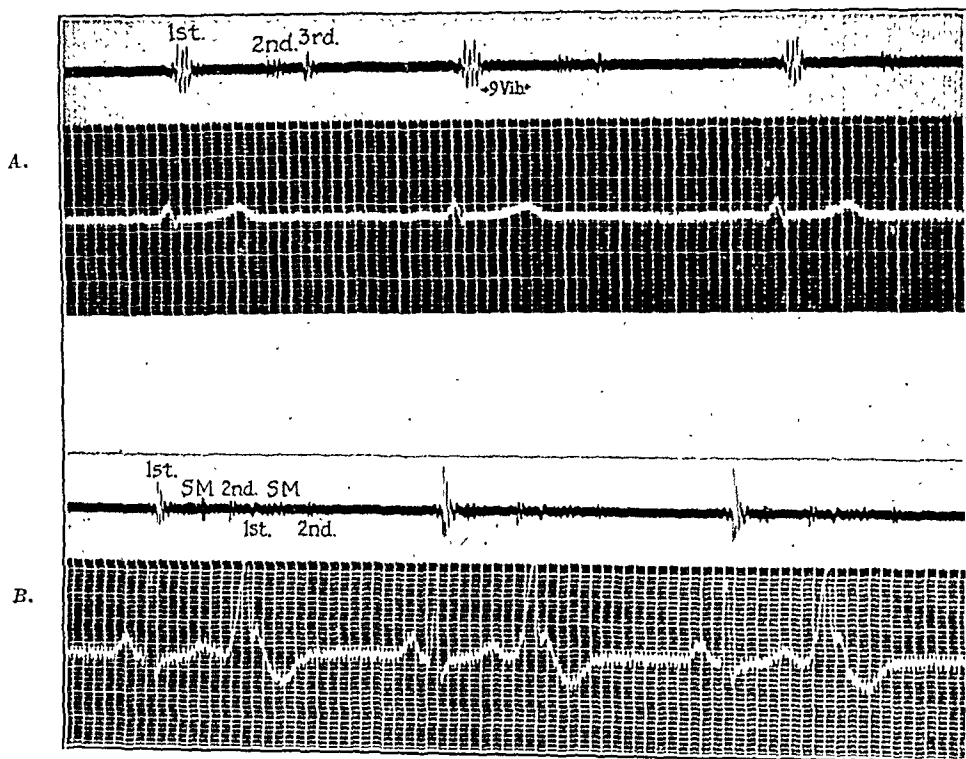


Fig. 2.—Stethograms showing: *A*, Normal heart sounds with nine vibrations following the first heart sound. *B*, Heart sounds from a patient with organic heart disease who had a systolic murmur (*SM*) and rhythmic bigeminy. The first sound of the ectopic beat was inaudible.

A study of body habitus showed that the inaudible systolic vibrations occurred more often in the asthenic type of individual.

Early diastolic vibrations were present in fourteen cases (12.7 per cent). The maximum number of vibrations recorded was 8 to 10. In no instance was a diastolic murmur audible through the stethophones.

It seemed advisable to compare the systolic vibrations found in our series of normal subjects with the records of known organic murmurs. A series of fifty cases of organic heart disease in which there were obvious systolic and diastolic murmurs was studied with the stethograph. These cases will be reported in detail at another time; however, it was ascertained that in the majority of cases an organic systolic or diastolic murmur was represented by 16 to 44 vibrations. Thus it became clear that 20 per cent of the total normal group (medical students) had 16 to 26 systolic vibrations that could not definitely be distinguished from

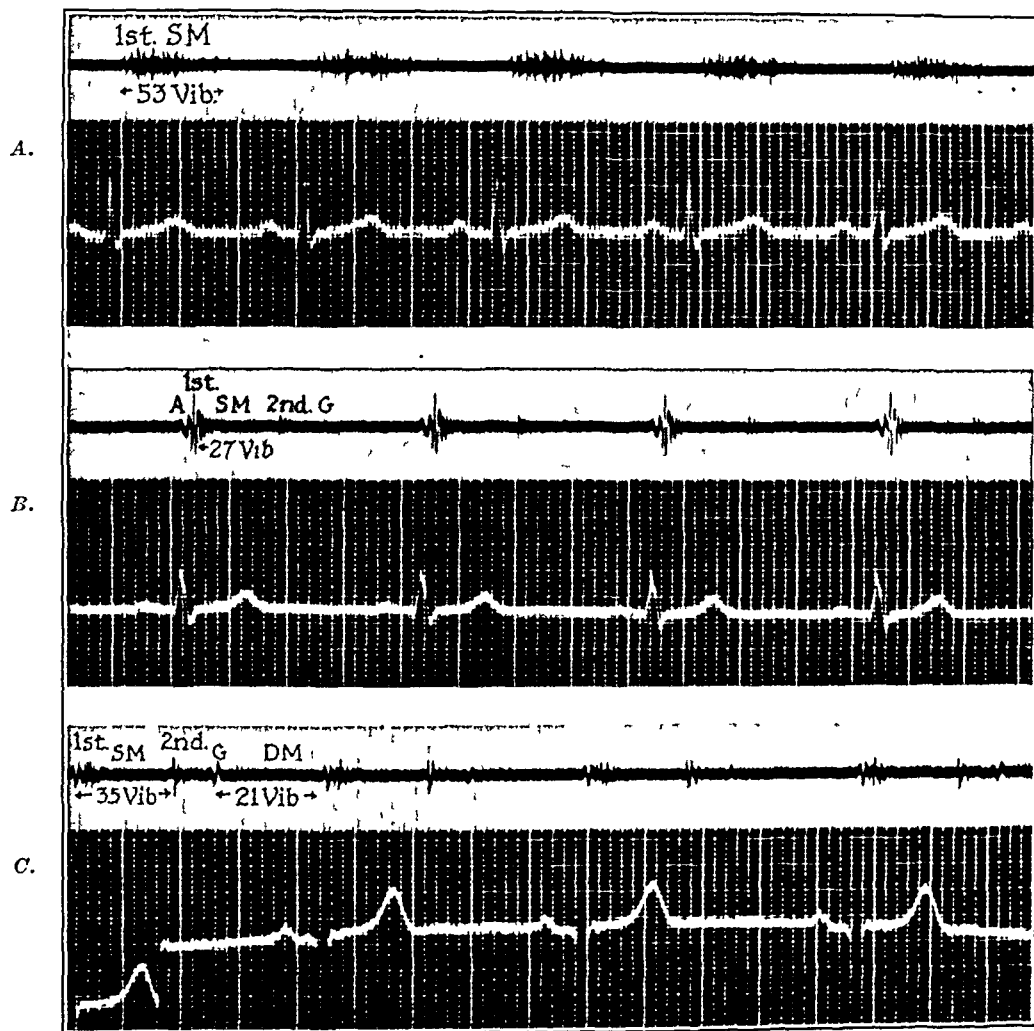


Fig. 3.—Stethograms from patients with organic heart disease showing: A, Apical systolic murmur comprising 53 vibrations (*SM*). B, Apical systolic murmur comprising 27 vibrations (*SM*) and protodiastolic gallop (*G*). C, Apical systolic murmur comprising 35 vibrations (*SM*), diastolic murmur comprising 21 vibrations (*DM*), and protodiastolic gallop (*G*).

the recorded murmurs of organic heart disease. However, the well-defined organic murmurs usually had more vibrations and were of longer duration. Some records of organic systolic murmurs simulated the stethograms showing systolic vibrations which were obtained from normal subjects (Fig. 3).

CONCLUSIONS

The characteristics and time relationships of the heart sounds of 110 normal young adults have been determined by means of the stethograph. The results suggest that, in the interpretation of stethographic records, systolic vibrations should not be regarded as actual murmurs unless there are at least sixteen regular oscillations. Clinical correlation is very important in the interpretation of cardiac sound records; it is not correct to interpret a few irregular oscillations in systole or diastole as a murmur, for they may be due to the impact of the apex against the chest wall, or to other extracardiac factors. Some genuine murmurs may be inaudible in the early stages of their development, but further research is necessary to determine the true significance of recorded vibrations when no sound is audible.

The authors wish to express their appreciation to Dr. J. G. Carr and Dr. A. C. Ivy for their help and constructive criticism in this study.

REFERENCES

1. Lockhart, M. L.: The Stethograph, *AM. HEART J.* 16: 72, 1938.
2. Martínez Cañas, J.: *Estetografía clínica*, *Vida nueva* 37: 287, 1936.
3. Martínez Cañas, J.: Los Ruidos diastólicos, *Rev. méd. cubana* 48: 1, 1937.
4. Horine, E. P.: An Evaluation of Electrical Heart Sound Records, *Kentucky Med. J.* 36: 432, 1937.
5. McKee, M. H.: Heart Sounds in Normal Children, *AM. HEART J.* 16: 79, 1938.
6. McKee, M. H.: Heart Sounds and Murmurs in Children with Rheumatic Heart Disease, *AM. HEART J.* 16: 88, 1938.
7. New York Heart Association: Criteria for Diagnosis and Classification of Heart Disease.

THE SIGNIFICANCE OF THE DURATION OF Q_3 WITH RESPECT TO CORONARY DISEASE*

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SINCE 1930, Pardee,¹ Durant,² and Wallace³ have offered various criteria for recognizing QRS changes which they considered highly significant of coronary disease. Their criteria, however, were concerned with amplitude only; they emphasized particularly the importance of a prominent Q_3 in association with a definite Q_2 . Primarily because of certain theoretical considerations, it seemed worth while to investigate the duration of Q_3 in a large number of electrocardiograms.

For this purpose 19,000 electrocardiograms recorded from adults were critically examined. At least one-third of the curves had been taken on negro subjects. The duration of Q_3 was measured along the top of the broad base line. Early in the study of these curves and of their related clinical data it became evident that a Q_3 of 0.03 second, or less, in duration was of little importance with respect to coronary disease unless there were also typical changes in the final ventricular deflections.

It was then decided arbitrarily to investigate further all curves of the 19,000 which presented an initial downward deflection in Lead III of duration equal to, or greater than, 0.04 second in at least five consecutive QRS complexes initiated by an impulse of auricular origin. All curves showing right axis deviation, all curves with QRS complexes of 0.11 second, or more, in duration, and all curves having M- or W-shaped complexes in Lead III were excluded.

The 163 electrocardiograms selected on the basis of these criteria were divided into two groups, according to the presence or absence of a Q_2 1 mm. or more in amplitude in at least five consecutive QRS complexes initiated by an impulse of auricular origin. Whether Q_3 was or was not followed by an immediate upward deflection was considered immaterial. This appears to involve the subject of terminology. The initial downward deflection under consideration may be regarded as an S_3 in curves in which there is no preceding Q_3 or R_3 , or may be looked upon as a Q_3 in curves in which R_3 is either present or absent. In order to avoid confusion, the notation adopted here is such that the initial downward deflection in Lead III is called a $(QS)_3$ deflection, thus indicating the independence of the presence or absence of an immediate subsequent upward movement.

The group of 163 curves contained 91 examples of the $Q_2(QS)_3$ and 72 of the $R_2(QS)_3$ variety.

*From the Department of Medicine of the School of Medicine, Louisiana State University, and the files of the Heart Station of Charity Hospital of Louisiana, New Orleans, La.

Received for publication March 22, 1939.

THE $Q_2(QS)_3$ GROUP

In each instance the clinical picture was one of heart disease. The chief findings displayed by the ninety-one patients are presented in Table I. In the compilation of the table, pain associated with exertion, excitement, cold, or heavy eating was considered a necessary part of the coronary disease picture in the absence of unequivocal "coronary" changes in both the initial and final ventricular deflections. Since coronary disease may be present in a patient not having these symptoms and electrocardiographic changes, the value of 82 per cent may be low.

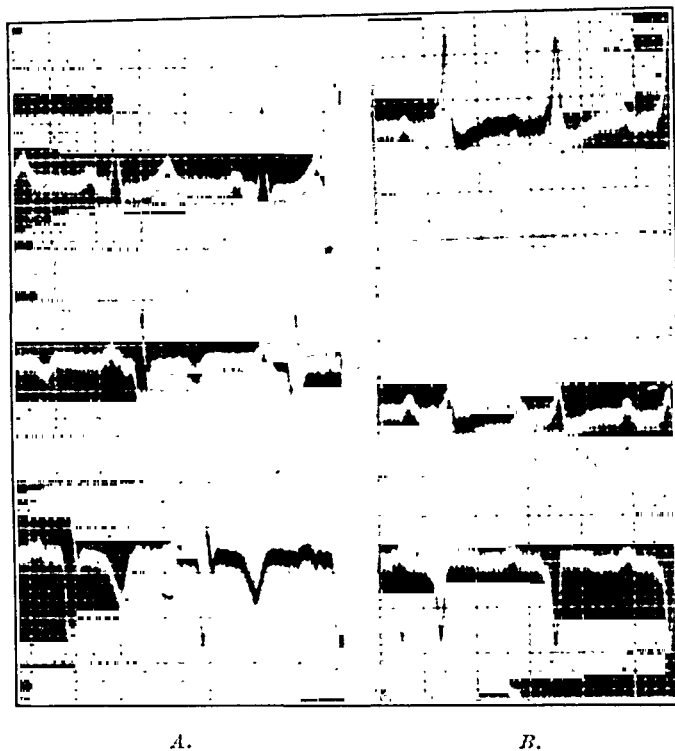


Fig. 1.—A, Sample curve of the type selected for the $Q_2(QS)_3$ group. B, Sample curve of the type selected for the $R_2(QS)_3$ group.

TABLE I

DISTRIBUTION OF 88 PATIENTS IN THE $Q_2(QS)_3$ GROUP ACCORDING TO THE ETIOLOGY OF THEIR HEART DISEASE. (THREE PATIENTS IN THIS GROUP, TWO WITH RHEUMATIC HEART DISEASE AND ONE WITH MYXEDEMA, ARE OMITTED FROM THE TABLE.)

HEART DISEASE	ARTERIOSCLEROTIC	HYPERTENSIVE	SYPHILITIC	TOTAL
Number with acute or sub-acute cardiac infarction	28	14	1	88
Number with pain caused by coronary disease	21	9	2	
Number without symptoms of coronary disease	2	6	5	
% of the etiological type with coronary disease	96	79	60	
% of $Q_2(QS)_3$ group with coronary disease	54	25	3	82

All of the subjects classified as having arteriosclerotic heart disease were white, and all but three were males. In more than half of the curves in this group, the amplitude of $(QS)_3$ was less than half as great as that of the largest QRS deflection. There was an 80 per cent incidence of abnormal changes in the final ventricular deflections. The most common type of RS-T junction and segment deviation was of the Q_3T_3 variety. One-fourth of these curves displayed a so-called coronary T in one or more leads. Auricular fibrillation was rare.

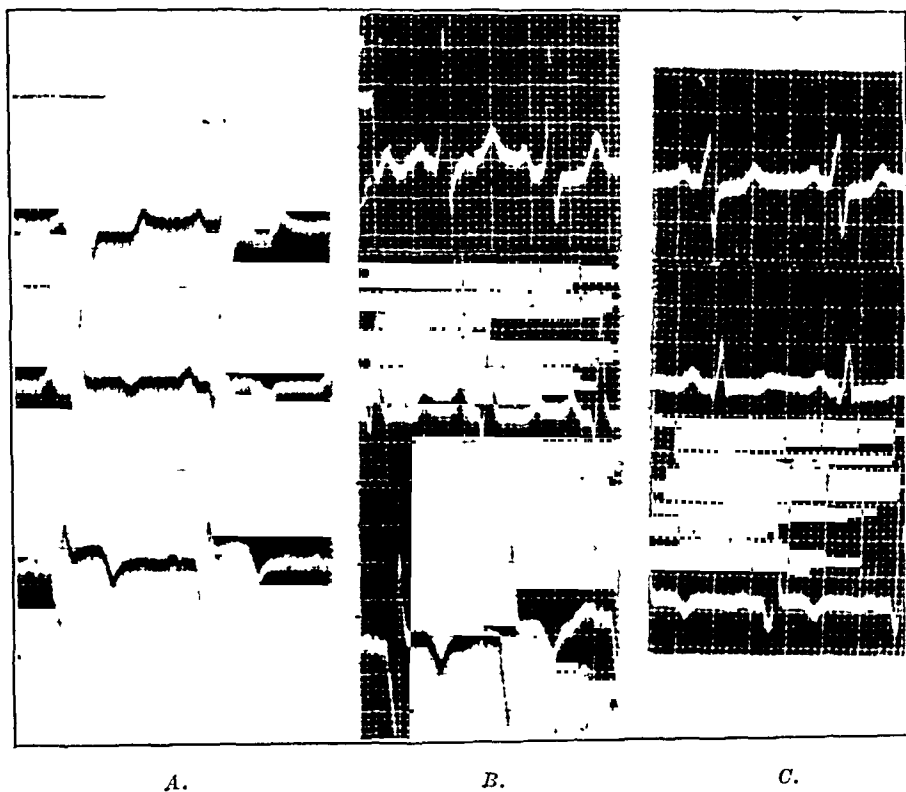


Fig. 2.—Curves A and B were recorded over a one-year period from a white woman, 49 years of age, and indicate the presence of a large posterior infarct. Curve C was recorded from this subject one and one-half weeks after a second (anterolateral) infarct.

THE $R_2(QS)_3$ GROUP

The criteria established for this group were identical to those laid down for the $Q_2(QS)_3$ group, except that there was no Q_2 . All but one of the seventy-two subjects presented a clinical picture of heart disease. It was found that twenty-one of the twenty-nine patients in the arteriosclerotic subdivision and eleven of the twenty-four patients in the hypertensive subdivision had, or had previously had, definite clinical manifestations of coronary disease. In the syphilitic subdivision five of the twelve patients presented this picture. There were four additional patients with rheumatic heart disease, one of whom had pain caused by coronary involvement. Of the remaining three patients in the $R_2(QS)_3$ group, one had neurocirculatory asthenia, one anemia, and the third was pregnant.

DISCUSSION

Of unusual interest was the case of a white woman, 49 years of age, in which the diagnosis of hypertensive heart disease, diabetes mellitus, and coronary arteriosclerosis had been established. Her electrocardiograms are shown in Fig. 2. Curves *A* and *B*, which were taken nine months before Curve *C*, indicate the presence of a large infarct in the diaphragmatic wall of the left ventricle. She developed symptoms of acute cardiac infarction one and one-half weeks before Curve *C* was taken and died a few days after this recording. Curve *C* resembles the previous curves in all essential particulars. A marked diminution in amplitude has occurred, however, in both Q_2 and $(QS)_3$. This, together with the changes in the clinical manifestations, was believed to indicate the development of an infarct of the anterior wall of the heart.

Necropsy revealed an old posterior, and a recent anterior, infarct of the inner half of the wall of the left ventricle. A strikingly similar course of events was observed in a case reported by Wilson.⁴

When the records of the $Q_2(QS)_3$ and $R_2(QS)_3$ groups were considered jointly and those eliminated in which a diagnosis other than acute or subacute cardiac infarct was justified, it was observed that there were five times as many of the related electrocardiograms in the $Q_2(QS)_3$ group as in the $R_2(QS)_3$ group. This observation corroborates the opinion, expressed independently by Durant and Wallace, that the presence of a Q_2 in addition to a prominent Q_3 lends further support to the presumptive diagnosis of coronary disease.

The criteria suggested for the $Q_2(QS)_3$ group appear to have an advantage over those offered by Durant, for they enable one to select, without loss of specificity, all of the curves which would be included on the basis of his most rigid QRS criteria, plus at least as many more additional curves.

SUMMARY AND CONCLUSIONS

1. A critical examination of 19,000 electrocardiograms led to the establishment of new criteria for recognizing QRS changes which are highly significant with respect to coronary disease.

2. Emphasis is placed upon a broad $(QS)_3$ of large amplitude which subsequently undergoes a sharp diminution in amplitude. This change alone is thought to be indicative of anterior infarction when it occurs in a patient who has already had infarction of the posterior wall of the heart.

REFERENCES

1. Pardee, H. E. B.: Significance of Electrocardiogram with Large Q in Lead III, *Arch. Int. Med.* 46: 470, 1930.
2. Durant, T. M.: Initial Ventricular Deflection of Electrocardiogram in Coronary Disease, *Am. J. M. Sc.* 188: 225, 1934.
3. Wallace, A. W.: Q Wave in Electrocardiogram, *Am. J. M. Sc.* 188: 498, 1934.
4. Wilson, F. N.: Diseases of the Coronary Arteries and Cardiac Pain, Ed. by Robert L. Levy, New York, 1936, p. 312, The Macmillan Co.

THE TREATMENT OF OCCLUSIVE ARTERIAL DISEASE OF THE LEGS BY MEANS OF THE SANDERS VASOCILLATOR (SANDERS BED)

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IN 1936, Sanders¹ described a motorized oscillating bed for the treatment of cardiac and vascular diseases. This bed has recently been described and accepted by the Council on Physiotherapy of the American Medical Association² under the name "Sanders vasocillator." In brief, it consists of an ordinary hospital bed attached to a special cradle, so that the bed can be rocked on a transverse axis across its midportion after the manner of a child's seesaw. By means of an electric motor the bed is tipped on this transverse axis continuously, so that the head of the bed is alternately raised and lowered through an arc of approximately 60 degrees. The period of oscillation can be adjusted to take from one to seven minutes for a complete cycle. It is possible to change the midposition of the bed through a small arc, so that, in the extreme positions, the head of the bed may be higher and the foot lower at the end of the cycle, or vice versa. The head and foot of the bed are hinged so that either can be raised, and the patient made to lie in the semirecumbent position with the thighs and knees partially flexed.

In cases of peripheral vascular diseases the therapeutic principle of this bed is simply the old principle of postural exercises, except that the changes in posture can be carried out for long periods without effort on the part of the patient and with a steady, continuous rhythm.

Sheard has devised a bed on the same principle, but with a different type of mechanism. The foot of the bed is raised and lowered through a fixed arc more rapidly than in the case of the Sanders vasocillator, but intermittently, the movement stopping at the maximal elevation and maximal dependency for certain periods. The period during which the bed is stopped can be varied from a few seconds to several minutes by a simple adjustment. An advantage of Sheard's bed is that the periods of elevation or dependency can be more easily varied. It possesses the disadvantage that patients are more conscious of the intermittent than of the continuous motion.

This report is based on observations of eighty-eight cases of occlusive arterial disease of the legs in which the patients were treated with these beds. The eighty-eight cases consist of thirty-eight cases of arteriosclerosis obliterans without diabetes mellitus, sixteen cases of arteriosclerosis obliterans with diabetes mellitus, thirty-one cases of thromboangiitis

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Received for publication April 8, 1939.

obliterans, two cases of embolic arterial occlusion, and one case of traumatic arterial occlusion. No difference could be observed in the effect of the bed in cases of different types of arterial lesions in which the symptoms and degree of arterial insufficiency were roughly the same.

In using the beds it was found that it was important to have the patient in a comfortable position, and to secure enough flexion of the thighs and knees so that when the head of the bed was at its maximal elevation the patient's body did not slip toward the foot of the bed. It also was found that adjustments of the bed were usually necessary for each patient, that it was usually advisable to run the Sanders bed at a rather rapid speed (cycle of two minutes), and that it was desirable to have the feet of the patient just become blanched when they were in the elevated position and just develop rubor when they were in the dependent position before the direction of motion changed.

PHYSIOLOGIC EFFECTS

The most obvious physiologic effect was the change in the color of the skin during the cycle of oscillation, which indicates that there were alternate filling and emptying of the capillaries in the skin of the feet and toes. Studies of the skin temperature were carried out on six patients before and after treatment with the bed (Table I). In general, it can be said that there was only a minor increase in the skin temperature, although this depended upon the degree of arterial obstruction in the extremity. The elevation in skin temperature was less than that produced by other vasodilating agents, such as typhoid vaccine and ethyl alcohol, in the same cases. In a series of cases oscillometric readings were taken before and after treatment with the bed. There was usually, but not always, a slight increase in these readings; this was less marked, or absent, in those cases in which the patients had severe degrees of arterial obstruction. One interesting effect of the bed was that the majority of the patients became rather sleepy after they had been on it for a comparatively short time, the oscillating movement apparently having a definite soporific effect. Since ordinary sleep causes vasodilatation, sleep may have been partly responsible for the rise in skin temperature.

IMMEDIATE EFFECT ON PAIN

On the basis of the symptoms and clinical observations the eighty-eight cases were divided roughly into four groups. Group 1 included sixteen cases in which intermittent claudication was the only symptom. Group 2 included thirteen cases in which pain occurred in the digits or feet while the patients were at rest (pretrophic pain). There was no evidence of ulceration, gangrene, or ischemic neuritis in this group of cases. Group 3 was composed of fifteen cases in which the patients had pain which was characteristic of ischemic neuritis. There was no evidence of ulceration

or gangrene in any of the cases in this group. In group 4 there were forty-four cases in which the patients had ischemic ulcers or gangrene and severe pain in the region of these lesions.

TABLE I
RISE OF SKIN TEMPERATURE AFTER TREATMENT WITH SANDERS BED
FOR 1.5 TO 2 HOURS

	CASE 1		CASE 2		CASE 3		CASE 4		CASE 5		CASE 6	
	LEFT FOOT	RIGHT FOOT	LEFT FOOT	RIGHT FOOT	LEFT FOOT	RIGHT FOOT	LEFT FOOT	RIGHT FOOT	LEFT FOOT	RIGHT FOOT	LEFT FOOT	RIGHT FOOT
Average rise in tempera- ture of skin of toes, de- grees C.	2.2	1.5	2.0	2.7	0.1	1.1	2.0		3.8	3.3	1.0	1.1
Average maximum tempera- ture of skin of toes, de- grees C.	32.5	32.3	33.0	33.7	29.7	28.5	31.2		32.4	32.2	29.7	28.6

The most striking effect of treatment with the bed was the relief of prethrophic pain, the pain of ischemic neuritis, and the pain which was associated with ulceration and gangrene. In twelve of the thirteen cases in group 2 the patients obtained complete relief from pain while they were on the bed. Similarly, of the fifteen patients in group 3, nine obtained complete relief of neuritic pain while they were on the bed, and four more obtained partial relief. In thirty-two of the forty-four cases in group 4 the patients obtained complete relief from pain while they were on the bed. A striking example was that of a woman who had hypertensive heart disease and auricular fibrillation. She had had arterial emboli in both legs; these emboli had resulted in complete arterial obstruction at a point just below the right knee, and progressive gangrene of the entire foot and leg developed. She suffered from severe pain in the region proximal to the upper margin of the gangrene. The pain could not be controlled by the administration of morphine, but she secured complete relief from pain while she was on the oscillating bed. Several times the bed was stopped in various positions, but each time the pain returned in a few minutes, and it was necessary to start the oscillation of the bed again in order to relieve the patient. In practically all instances in which relief from pain was obtained, the pain recurred after the patients were taken off the bed during the early periods of treatment. Many patients stated that while they were on the bed they were able to sleep without the help of drugs for the first time in several weeks.

RESULTS OF PROLONGED TREATMENT

The persistent effects of the treatment on the symptoms and manifestations of arterial insufficiency were somewhat difficult to evaluate. Of the

eighty-eight patients, some were treated only one hour a day for comparatively short periods, whereas others were treated more intensively for long periods, and still others were kept on the bed practically continuously for several days or weeks. Some of the eighty-eight patients were given other types of treatment during the period that they were being treated with the bed. In trying to evaluate the results an attempt was made to be conservative. Most of the patients were not ambulatory, and some of the improvement noted may have been simply the result of rest in bed, warm environmental temperatures, and the natural tendency of the circulation of the extremities to improve in the absence of further episodes of arterial occlusion.

Group 1.—In eight of the sixteen cases in group 1 a definite improvement was noted, but it was felt that this was due to other types of treatment. In general, there appeared to be no definite improvement with respect to intermittent claudication following treatment with the bed.

Group 2.—In eleven of the thirteen cases in this group relief of pain persisted after the treatment was discontinued. In five of these eleven cases the patients were treated only with the bed. The other six patients received other types of treatment which may well have produced the same results if the bed had not been used. However, it is not certain that this would have occurred.

Group 3.—In nine of the fifteen cases in group 3 relief of pain persisted after the treatment was discontinued. In seven of these nine cases the patients were treated only with the bed.

Group 4.—In twenty-two of the forty-four cases in group 4 the ulcers or gangrene healed and the patients obtained complete and persistent relief from pain. In twelve of the twenty-two cases (eight cases of arteriosclerosis, two cases of thromboangiitis obliterans, and two cases of arterial embolism) the patients were treated only with the bed, except for the use of bland, warm, foot soaks and warm environmental temperatures. In the other ten cases all of the patients had thromboangiitis obliterans, and, in addition to treatment with the bed, typhoid vaccine was administered intravenously. In these cases the healing of the lesions and relief of pain were probably, although not certainly, due to the injections of foreign protein rather than to the effect of the bed.

COMMENT

In summarizing the effects of treatment in the seventy-two cases in groups 2, 3, and 4, it can be said that persistent good results were obtained in twenty-four, or 33.3 per cent. In these cases the patients were treated only with the bed. Persistent good results also were obtained in eighteen other cases but in these cases the results may well have been due to the other types of treatment which were given simultaneously. No persistent benefit was obtained in thirty, or 41.7 per cent, of the seventy-two cases, regardless of whether the bed was used alone or in conjunction

with other types of treatment. In this paper we have used the term "persistent good results" to mean relief from pain and healing of ulcerative or gangrenous lesions which persisted for a period of at least six months after the treatment was stopped. It is well known that patients with occlusive arterial diseases of the legs may have relapses due to occlusion of other arteries.

A few other observations are worth mentioning. In five of seven cases of comparatively recent acute arterial occlusion and marked ischemia, there was definite evidence of improvement of the circulation after a few days of intensive treatment. In one of these cases the patient was a man who had had thromboangiitis obliterans for ten years. He entered the hospital two days after the occurrence of acute arterial occlusion. He had moderately severe pain in his right foot. There was a definite reduction of sense perception in the distal half of the foot, which was cold and shrunken. The foot became completely blanched on elevation, and on dependency after elevation the color did not return in the skin of the toes until two minutes and fifteen seconds had elapsed. He was treated with the bed alone for twenty-three out of each twenty-four hours. After four days the color returned in the foot forty-five seconds after dependency during the elevation-dependency test. Sense perception returned to normal, and the pain was completely and permanently relieved.

It is interesting to note that, when the bed was satisfactorily adjusted, we did not observe any case in which the pain became worse while the patient was on the bed, and untoward effects from treatment on the bed were noted in only one case. In this case the patient had thromboangiitis with gangrene of a toe and beginning gangrene of the distal portion of the foot. After treatment on the bed had been continued for two days, an ascending lymphangitis of the leg developed. We are not certain whether this was due in any way to treatment with the bed. In thirty-four cases it was possible to make some comparison between the effects of treatment with the bed and the effects of treatment with the intermittent suction and pressure machine. Of these thirty-four patients, seven who were unable to tolerate the suction pressure machine because it aggravated their pain obtained relief with the bed. Fourteen other patients felt that they had obtained definite relief from pain while they were on the bed, whereas they had not obtained any relief from pain with suction and pressure. Three patients felt that suction and pressure had produced definite relief from pain, while the bed had not. Nine patients felt that they had been relieved both by suction and pressure and by the bed in an approximately equal degree, and eight patients felt that neither the suction and pressure nor the bed had relieved their pain.

SUMMARY

The following is an attempt to summarize the value of the Sanders bed in the treatment of occlusive arterial diseases of the extremities, based on

the effects observed in the eighty-eight cases. We have found no contra-indications to the use of this method of treatment, with the possible exception of the presence of marked infection in association with gangrene. The bed can be used for comparatively short periods, or patients can be kept on it continuously for days or weeks. In comparison with other mechanical methods of treatment of peripheral circulatory diseases, it possesses the advantage of avoiding any constriction of the leg or obstruction to the venous circulation. It can be used in conjunction with vasodilating procedures, such as artificially induced fever, drugs given by mouth, or increased environmental heat. To secure the best effects, it is necessary to vary the position and timing of the cycle in accordance with the needs of the individual patient. This form of treatment produces slight objective improvement in circulation, and slight, but incomplete, vasodilatation. Its most striking therapeutic effect appears to be the immediate relief of pretrophic pain, the pain of ischemic neuritis, and the pain of ulceration and gangrene. Relief of these types of pain is not necessarily maintained when the treatment is discontinued. The bed apparently has minimal, if any, beneficial effects on the pain which causes intermittent claudication. It constitutes a valuable addition to the armamentarium for the treatment of peripheral arterial diseases, but it should not supplant other methods of treatment.

REFERENCES

1. Sanders, C. E.: Cardiovascular and Peripheral Vascular Diseases; Treatment by Motorized Oscillating Bed, J. A. M. A. 106: 916, 1936.
2. Report of the Council on Physiotherapy, J. A. M. A. 111: 2016, 1938.

THE SYNDROME OF SUPERIOR VENA CAVAL OBSTRUCTION

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CLINICAL and pathologic reports of obstruction of the superior vena cava are uncommon. Ehrlich, Ballou, and Graham,¹ in 1933, were able to collect from the entire literature only 309 cases. Minor degrees of compression of the superior vena cava are probably much more common than the comparatively small number of these reports would lead one to believe. A slight compression may cause no symptoms, and the signs may be so meager that either they are disregarded or overlooked entirely. Major obstructions by neighboring mediastinal tumors are probably also not as uncommon as the small number of reports in the literature suggests, because the symptoms of venous obstruction are to a considerable extent masked by more obvious and distressing symptoms, such as dyspnea and dysphagia, caused by pressure on other mediastinal structures. Furthermore, the obstruction is rarely complete, or of sufficiently long duration, because of the nature of the lesion causing it, to necessitate the development of a collateral circulation. On the other hand, occlusion of the superior vena cava without a demonstrable tumor in the mediastinum is rare. Survival, with the development of an adequate collateral circulation, is still more rare.

The following case is reported to illustrate the complete syndrome of occlusion of the superior vena cava, and to demonstrate the value of roentgenographic visualization of the vascular system, of segmental circulation time studies, and of venous pressure measurements in the diagnosis of such an obstruction.

REPORT OF CASE

L. G., a man 30 years of age, first came to the Outpatient Medical Department of the Temple University Hospital because of a buzzing sensation in both his ears. Upon examination, many enlarged subcutaneous veins were seen over the upper half of his body. He entered the Temple University Hospital Jan. 9, 1939. The following history was obtained:

The patient was born in Russia, and as a child had scarlet fever, measles, chicken pox and typhus fever. He came to America at the age of 9 years and had always lived either in Philadelphia or New York City. Ever since adolescence he had worked as a paperhanger. He had been well until 1929, when he was 21 years old. At that time he was in New York City. He felt well and considered himself so until his friends told him that his face and neck were swollen to one and one-half times normal size and that his face had taken on a peculiar, greenish-red (cyanotic?) color. At first he paid no attention to this, but within a week he himself noticed the change, and at the same time he observed that his eyes were becoming very prominent and appeared as if they would pop out of his head. All through the day and night he

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Received for publication April 10, 1939.

was disturbed by peculiar "machinery-like" noises in his head. This drove him finally to seek medical attention. He entered St. Luke's Hospital, in New York City, Oct. 8, 1929, and was discharged Dec. 24, 1929. During his stay in the hospital he had an intermittent fever with recurrent chills and sweats. Because of his frequent complaints of headache, a spinal puncture was done, and the cerebrospinal fluid was found to be under increased pressure. (The details of the clinical and laboratory studies are not available.) He felt well upon discharge and soon began to notice prominent veins over the upper half of his body. These continued to increase in size.

He regarded himself as well until one month before admission to the Temple University Hospital. At that time he developed a buzzing in his ears. This buzzing was synchronous with the heart beat, was aggravated by emotional upsets, exercise, and the assumption of the upright position, and was improved by rest and lying down. He stated that he often had occipital headaches, that his eyes frequently became bloodshot, and that he developed diplopia when he hyperextended his head.

Physical examination revealed a well-built, well-nourished young man. There was nothing of note in the entire examination, including the ear drums, except for the presence of the large subcutaneous veins. The heart was entirely normal in size, shape, and position, as judged by physical and fluoroscopic examination; the sounds were regular and normal. The electrocardiogram was normal. There was no evidence of a mediastinal tumor. The liver and spleen were not palpable. There was no fluid in the abdomen and no edema of the legs.

The veins of the head, particularly the postauricular, were engorged and enlarged, even in the standing position. The neck veins were likewise enlarged and distended with blood. There were numerous tortuous, dilated, overfilled veins in both the upper extremities, on the anterior and lateral chest walls, and over the abdomen. Particularly prominent were the lateral thoracic veins on both sides. There were no prominent veins over the back or in the lower extremities. It could be easily demonstrated that the lateral thoracic veins emptied caudally into the superficial epigastric veins. This was true in the recumbent position even when the pelvis was elevated by one pillow.

The venous pressure in both upper extremities was measured by the direct von Tabora and Moritz method. The pressure in the right arm, taken in the antecubital vein in the supine position, with the arm abducted to forty-five degrees, and with the zero point adjusted to two and one-half inches dorsal to the angle of Louis,² was 17.4 cm. of saline; in the left arm it was 19.8 cm. of saline. These pressures could be raised to 22.5 and 28 cm., respectively, by compressing the thoracic or abdominal veins on the homolateral sides, indicating a definite connection between the veins of the arms and those of the thorax and abdomen. The saccharine time, according to the method of Hitzig, was 32 seconds in the left arm, and 22.4 seconds in the right. These times could be prolonged to a variable extent by exerting more or less pressure on the veins of the thorax and abdomen on the homolateral sides. This indicated that the increase in circulation time was due to the fact that the returning venous blood had to traverse an abnormally long course, rather than to cardiac failure. The venous pressure in the legs was 8.5 cm. of saline.

The presence of prominent veins over the upper half of the body with venous hypertension limited to this area and of retrograde flow of blood in the thoracic and abdominal veins, together with the fact that both the venous pressure and the circulation time could be increased by compressing the thoracic or abdominal veins, established the diagnosis of complete obstruction of the superior vena cava, or of both innominate veins, with or without obstruction of the immediate tributaries.

It was decided to attempt to follow the circulation of the blood by means of some substance which the patient could sense. Five c.c. of a mixture of equal parts of a

20 per cent magnesium sulfate and a 10 per cent calcium gluconate solution were injected rapidly into the left antecubital vein. The patient felt a creeping and warm sensation, successively, in the left shoulder (one second), left axillary region (two seconds), simultaneously in the left precordial area and left upper quadrant of the abdomen (five seconds), in the left lower quadrant of the abdomen (six seconds), heel (eight seconds), hypogastrium (ten seconds), and epigastrium (eleven seconds). This sequence is correct, but the exact time relationship is probably not accurate because of overlapping in the perception of the sensations. A similar injection in the right antecubital vein produced the same sequence of sensations on the right side of the body. From this sequence of events one would assume that the flow of blood was from the antecubital vein to the axillary and lateral thoracic; part then went to the intercostals and internal mammary, and part to the superficial epigastric, femoral, iliac, and inferior vena cava or azygos. No adequate explanation for the sensation in the heel can be given. These tests were repeated several times, and



Fig. 1.—Photograph of the patient, showing the large lateral thoracic and abdominal veins.

each time the patient felt a creeping and warm sensation in the heel at approximately the same interval and in the same sequence. No sensation was perceived in the face or neck. As a matter of fact, no adequate explanation can be given for any of the sensations perceived, because these results differ fundamentally from those ordinarily obtained. Clinical circulation-time studies depend upon the transportation of a foreign substance to some special sense organ, whereas in this instance the passage of the foreign body was detected by the patient while it was still in the veins. There are apparently only two possible explanations for this. Because of the venous hypertension, the foreign substance may have diffused through the veins to

the skin. This seems very unlikely. The other explanation is that the veins may have acted as receptor end organs. The only reference to this possibility that I could find was in the monograph by Franklin.³ Further studies on this question are contemplated.

It was decided to attempt to visualize the abnormal venous communications radiologically. Diodrast was injected into one of the large antecubital veins by means of a large 16-gauge needle, with the arm extended above the head. This injection was completed as rapidly as possible, and two stereoscopic roentgenograms were made on one day in the right anterior oblique position, and on another day in the anteroposterior position, in each instance two and six seconds, respectively, after the beginning of the injection. On the first day 40 c.c. of a 35 per cent solution of diodrast were used, and on the second day, 35 c.c.



Fig. 2.—Right anterior oblique view, visualizing the veins with diodrast.

Dr. R. P. Meader of the department of radiology of Temple University Hospital interpreted the films. The following is an excerpt from his report:

Right anterior oblique view: "It is probable that the three veins draining the right arm are the cephalic, brachial, and basilic. Anastomoses distal to the point of visualization probably account for the fact that all three are visible. The junction of the basilic and brachial veins, forming the axillary vein, is visualized, but the axillary vein is not visible proximal to the region of the second rib. Instead, there appears to be a definite connection between the junction of the basilic and brachial veins and the lateral thoracic, forming the enlarged superficial vein which is so tortuous down the lateral aspect of the thorax. This continues into the thoracoepigastric, which communicates with the superficial epigastric over the abdomen. The thoracoepigastric vein appears to drain into the intercostal vein on the right

which lies immediately beneath the sixth rib. This is the only one of the intercostals which seems to be connected with this superficial vein.

"The cephalic vein is visualized crossing the right clavicle and proceeding mesially between the clavicle and the first rib. As stated above, the junction of this cephalic vein with the axillary is not clearly seen. Communicating with the continuance of the cephalic vein near the anterior chest wall and proceeding caudally along the axis of the spine, there is a pair of veins which appear to be venae comitantes and are probably the internal mammary veins with an artery between them. These connect with the upper intercostal veins, some of which are well visualized."

Anteroposterior view: "Although the clinician has not stated into which vein the material was injected at this examination, he probably did not use the same antecubital vein as before. This is thought to be true because there is no evidence of visualization of the cephalic or subclavian vein, or of the venae comitantes which were previously regarded as the internal mammary veins.

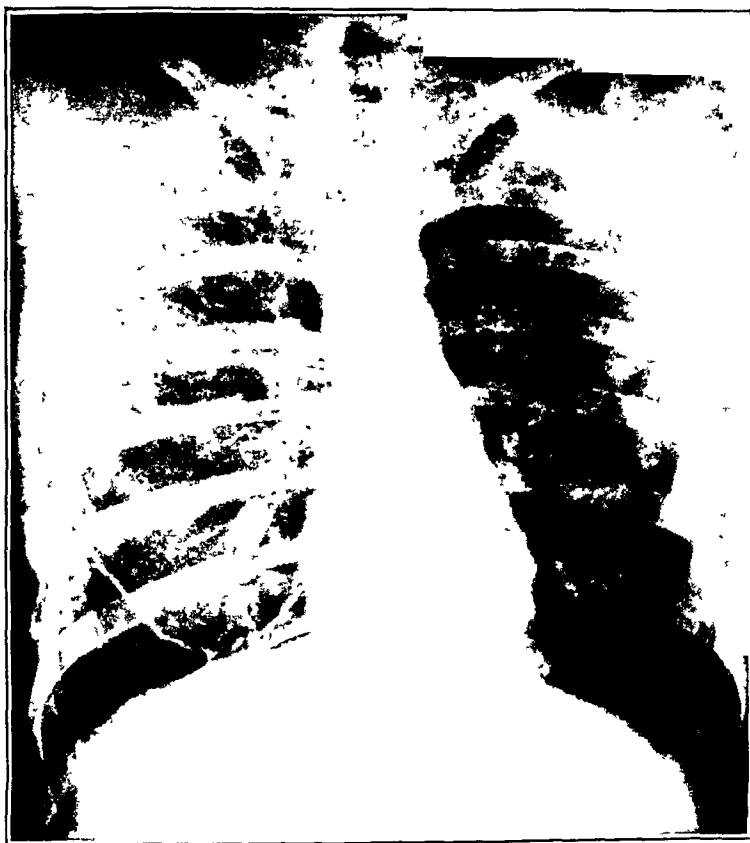


Fig. 3.—Anteroposterior view, visualizing the veins with diodrast and demonstrating the absence of a mediastinal lesion.

"These posteroanterior roentgenograms, which were made two and six seconds, respectively, after the beginning of the injection of the diodrast, show what appears to be the brachial vein emptying into the lateral thoracic vein, which then proceeds in a tortuous fashion down the lateral aspect of the thorax. A branch of this lateral thoracic seems to penetrate the chest wall under the sixth rib in the anterior axillary line and to proceed posteriorly in the region of the sixth intercostal vein. It may be that a branch of this vein also goes anteriorly along the sixth rib, but I believe that the other, smaller veins which are visualized over the lower thoracic wall are probably superficial to the chest wall."

DISCUSSION

The superior vena cava may be partly or totally obstructed, with or without thrombosis, by any mass in the mediastinum. It may also be obstructed by a foreign body or a thrombus. The commonest causes of obstruction are aneurysm of the aorta and malignant tumors. The rarest cause is thrombosis. The following outline enumerates the various causes for superior vena caval obstruction.

1. Aneurysm of the aorta: This may compress the vena cava or may actually rupture into it. The characteristic manifestations of rupture include not only the suddenness of the onset, but also the development of a new, continuous murmur and pulsations in recently enlarged veins of the upper half of the body.⁴
2. Mediastinal tumors
 - a. Lymph node enlargement: metastatic carcinoma, leucemia, Hodgkin's disease, inflammatory hyperplasia (syphilis, tuberculosis, granulomata, nonspecific)
 - b. Thymus gland enlargement
 - c. Thyroid gland enlargement
3. Mediastinitis
4. Pericarditis, with or without effusion
5. Cysts
6. Trauma, due to hemorrhage
7. Thrombosis

Thrombosis of the superior vena cava is also the rarest of all venous thromboses. In an exhaustive review of the literature, Ochsner and Dixon⁵ found reports of 120 cases. In not all of these was the diagnosis definitely proved. Of these 120 cases, external compression was the cause in 35 (29.1 per cent); mediastinitis in 28 (23.3 per cent); the cause was either unknown or not stated in 13 (10.8 per cent); and phlebitis was the underlying lesion in 44 (36.6 per cent). Of the 44 cases of phlebitis, syphilis was the cause in 12, tuberculosis in 4, a pyogenic process in 7, and trauma in 1; 10 of the patients had heart disease, and in 10 cases the phlebitis was of unknown origin. Therefore, only ten cases of idiopathic phlebitis with superior vena caval thrombosis had been reported. Since that time one case of tuberculous phlebitis has been reported by Szour and Berman⁶ and one of phlebitis of unknown origin by Blasingame.⁷

In the case reported herein, the presence of venous hypertension in the head, neck, and upper extremities indicated obstruction of the superior vena cava and both innominate veins. The roentgenographic demonstration of obstruction of the axillary veins excluded the possibility that a simple encircling band at the base of the superior vena cava was the cause. The only plausible explanation was thrombosis of the superior vena cava extending into its main tributaries, including the axillary

veins. The old history of fever, chills, and sweats suggested that the thrombosis was of infectious origin. The nature of this infection is entirely conjectural. An interesting report of thrombosis of the superior vena cava following influenza was reported by Strauss.⁸ This is the twenty-fifth case of superior vena caval thrombosis not due to a mediastinal tumor.

The development of a collateral circulation depends on the site of occlusion of the superior vena cava, i.e., whether it is above or below the azygos vein.

Carlson's⁹ experiments on dogs showed that when the occlusion is above the azygos, the superficial veins show the following anastomoses. The axillary unite with the thoracoepigastric to join the plexus over the thorax and abdomen. The veins of the neck anastomose with those of the thorax and empty into the intercostal veins. They also communicate with the superficial epigastric and the superior and inferior epigastric, to unite with the femorals and the external iliac.

The deep veins go from the internal mammary to the intercostals, to the anterior mediastinal, and to the superficial epigastric. There is, furthermore, an anterior and posterior plexus of mediastinal and pericardial veins which empty into the subphrenic and the tributaries of the inferior vena cava. There is also a connection above, through the vertebral column, with the dural sinus and the vertebral veins, and below with the intervertebral and intercostal veins, the deep dorsal veins of the back, the posterior rami of the intercostal veins, and the descending branches of the transverse cervical and scapular veins.

The lumbar veins join the abdominal and suprarenal and the superficial and deep veins of the back; some of them empty into the azygos.

The superficial intercostal and the other intercostals join the accessory hemiazygos and azygos veins.

In this type, the azygos vein, with its tributaries, is greatly enlarged, and becomes the principal channel through which the blood returns to the heart.

When the occlusion is below the azygos, the superficial veins are prominent over the abdomen and thorax. The deep veins go from the internal mammary to the superior and inferior epigastric, to the external iliac veins. There is a rich anterior and posterior mediastinal and pericardial plexus. The vertebral venous plexus is extensively developed; in particular, the internal and the deep collaterals of the back are present.

To summarize Carlson's conclusions, when the occlusion is above the opening of the azygos veins, the azygos vein and its tributaries form the chief channel for the return flow of blood from the upper part of the body to the heart. The lower abdominal collateral veins are relatively unimportant. In the second type, when the occlusion is below the opening of the azygos vein, the superficial and deep abdominal vessels and vertebral plexus are of much greater importance. All of the blood returns to the heart through the inferior vena cava.

In addition to the above collaterals, one must also, according to Ochsner and Dixon,⁵ consider the anastomoses between the esophageal and gastric coronary veins and the inferior vena cava.

A beautiful example of the collateral circulation in a case of superior vena caval thrombosis was recently published in the *Archives of Pathology*, and the diagram is reproduced with the kind permission of the author.¹ The lesion was found in the dissection of a cadaver; the body was that of a man 93 years of age, and no history was obtainable.

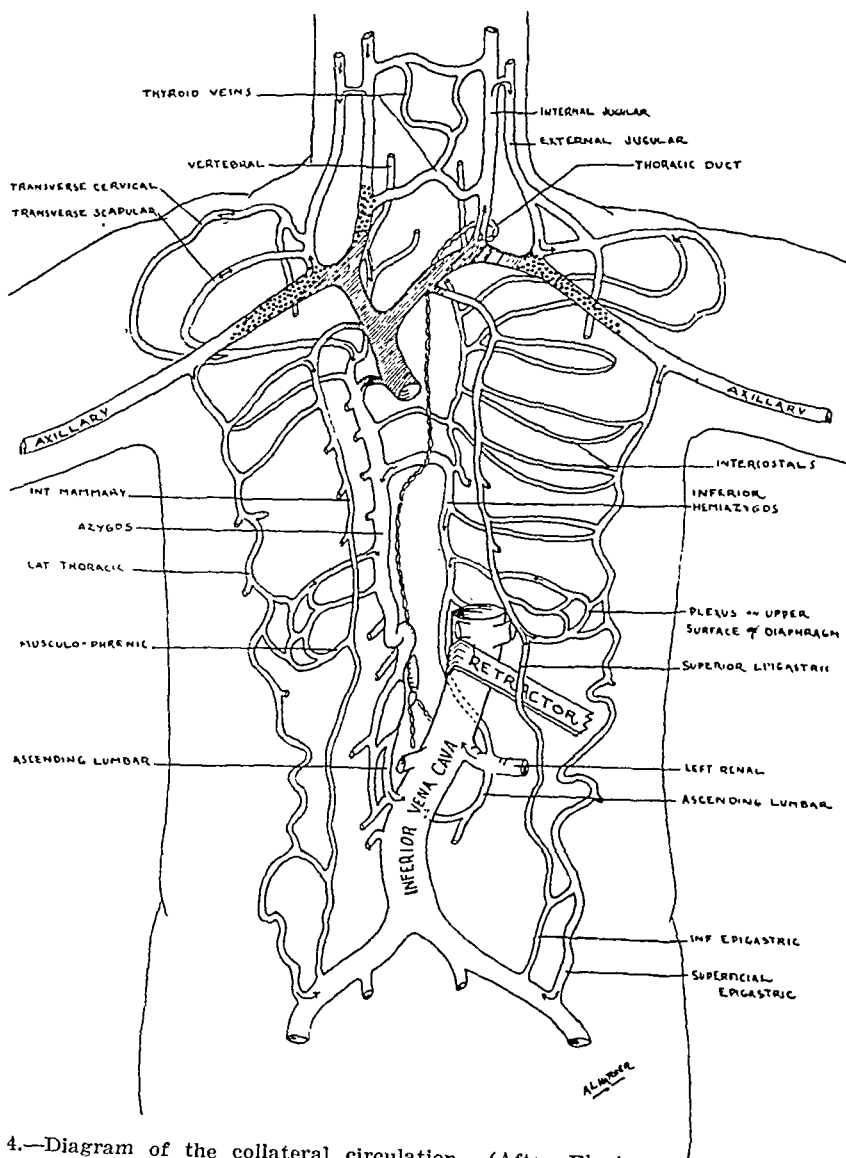


Fig. 4.—Diagram of the collateral circulation. (After Blasingame, with kind permission of the author.)

This case appears to be practically identical with mine, because, as is seen in the diagram, there were complete obstruction of the superior vena cava and the innominate veins and partial obstruction of the axillary veins.

Obstruction of the superior vena cava may occur at any age, but it is most common in the fourth and fifth decades. It occurs with equal frequency in the two sexes. The symptoms depend on the degree of occlusion, the rapidity of its development, and the absence or presence of a collateral circulation. With lesser degrees of obstruction there may be no symptoms, and the diagnosis is made by demonstrating that there is increased venous pressure localized to the upper half of the body. This will be discovered more and more frequently if routine venous pressure measurements are made in all patients suspected of having or known to have mediastinal lesions.¹⁰ In slow, gradual, complete occlusion, there may be no symptoms because the development of the collateral circulation keeps pace with the occlusion. In sudden, complete occlusion, the symptoms caused by congestion of the veins emptying normally into the superior vena cava are dramatic. The superior vena cava returns the blood from the head, face, neck, upper extremities, thoracic walls, and a portion of the upper part of the wall of the abdomen. If the occlusion is sufficient in degree and rapid enough in its development, the patient develops cyanosis and edema of the head, face, neck, and perhaps of the upper portion of the chest and upper extremities. The eyes become prominent, and, if the lesion is sufficiently acute, hemorrhages may occur in the retina and conjunctiva. The intracranial congestion produces peculiar noises throughout the head, disturbs the sensorium, and may cause tinnitus, deafness, papillary edema, somnolence, epistaxis, and, rarely, hemoptysis. The pressure of the cerebrospinal fluid is increased. At the height of the obstruction, the patient sits up and arches his back forward for relief from dyspnea. Fatal edema of the larynx¹¹ may occur, or death may be due to increased intracranial pressure and anoxemia of the brain. Pleural effusion occurs occasionally. Chylothorax has been produced by experimental occlusion of the superior cava (Blalock, Cunningham, and Robinson¹²) but has not been reported in man. About 75 per cent of the patients die during the acute stage.⁵ If the acute stage is survived, the symptomatology will depend upon the amount of collateral circulation. If this is adequate, there may be no symptoms, and the condition is not incompatible with life, as shown in the case of Blasingame's patient, who lived to the age of 93 years. Because of the continuously dilated intracerebral veins, cerebral symptoms, such as headache, tinnitus, vertigo, and even lethargy, are common. These symptoms are usually aggravated by sitting or standing and by exercise, and they are relieved by rest and lying down. Dryness and edema of the skin and dermatoses with itching lesions are occasionally seen in the upper half of the body.

A history of edema and cyanosis of the head, neck, and upper extremities should lead one to suspect superior vena caval obstruction. The presence of venous hypertension in the upper half of the body clinches the diagnosis. The subsequent development of enlargement of

the veins in the upper half of the body, in which the flow is retrograde, and, as shown by means of circulation time and venous pressure studies, with circulatory connections on the homolateral side, completes the demonstration. The symptoms, if any, are due to the lack of adaptability of the skull to this increased pressure. Wagner¹³ claims, after studying four cases by the injection method in the human cadaver, that dilatation of the dorsal thoracic veins suggests occlusion, in addition, of the azygos vein. Lian and Abaza¹⁴ state that an increased venous pressure in the upper half of the body, with a normal circulation time, is diagnostic of this condition. As shown in our case, this is not so, and cannot be so if the vena cava is completely occluded. It may be true if the occlusion is not complete, but it is important to remember that the venous pressure in both upper extremities may be elevated by local pulmonary disease, such as tuberculosis. However, in these cases there is no elevation of pressure in the veins of the head or neck unless there is compression of the superior vena cava caused by mediastinal tuberculosis.

The prognosis depends upon the rapidity of development and degree of the obstruction, as well as on the underlying cause. Of those patients with thrombosis of the superior vena cava, 75.9 per cent⁵ die in the acute phase. About the same percentage of patients with complete occlusion of the superior vena cava due to mediastinal tumor will die. Partial occlusion is not incompatible with longevity. Once an adequate collateral circulation has formed, the obstruction itself is comparatively unimportant, although most patients will complain of minor, usually cerebral, symptoms. Judging from the experimental work of Carlson,⁹ occlusion of the superior vena cava below the azygos vein is more serious than occlusion above the azygos vein and is rarely outlived.

The treatment depends upon the cause. In the acute occlusions caused by mediastinal tumors, roentgentherapy may be tried for radiosensitive lesions, and mediastinotomy for radioresistant lesions. The indication for treatment in cases in which the occlusion is the result of intravascular disease is to relieve the venous pressure in the tributaries of the superior vena cava. This can be done by bleeding, probably best from the jugular veins, and by placing the patient in the proper position. The most favorable position is the recumbent, with the head slightly lowered. Lumbar puncture may be of some help. In the chronic stage the treatment depends upon the severity of the symptoms. Usually no treatment is necessary except occasional sedatives.

CONCLUSION

A case of obstruction, probably caused by infectious thrombosis, of the superior vena cava and its main tributaries is presented. The literature is briefly reviewed, and the diagnostic criteria for this lesion are given.

I am indebted to Dr. Hugo Roesler for suggestions in studying this patient roentgenologically and in the preparation of the manuscript.

REFERENCES

1. Ehrlich, W., Ballou, H. C., and Graham, E. A.: Superior Vena Caval Obstruction with a Consideration of the Possible Relief of Symptoms by Mediastinal Decompression, *J. Thoracic Surg.* 3: 352, 1933.
2. Griffith, G. C., Chamberlain, C. T., and Kitchell, J. R.: Observations of the Practical Significance of Venous Pressure in Health and Disease, *Am. J. M. Sc.* 187: 642, 1934.
3. Franklin, K. J.: A Monograph on Veins, Springfield, Ill., 1937, Charles C. Thomas.
4. Armstrong, E. L., Coggin, C. B., and Hendrickson, H. S.: Spontaneous Arteriovenous Aneurysms of the Thorax, *Arch. Int. Med.* 63: 298, 1939.
5. Ochsner, A., and Dixon, J. L.: Superior Vena Caval Thrombosis, *J. Thoracic Surg.* 5: 641, 1936.
6. Quoted by Blasingame.⁷
7. Blasingame, F. J. L.: Thrombotic Occlusion of Superior Vena Cava, Associated With Established Collateral Circulation, *Arch. Path.* 25: 361, 1938.
8. Strauss, A.: Thrombose der oberen Hohlvene nach Grippe, Tod nach 10 Jahren, *Schweiz. med. Wchnschr.* 59: 1410, 1929.
9. Carlson, H. A.: Obstruction of the Superior Vena Cava: An Experimental Study, *Arch. Surg.* 29: 669, 1934.
10. Hussey, H. H.: The Effect of Mediastinal Lesions on Pressures in the Antecubital and Femoral Veins, *AM. HEART J.* 17: 57, 1939.
11. Boonacher, A. A.: Un Cas Rare d'Oedeme du Larynx par Stase Veineuse, *Rev. de laryng.* 53: 1064, 1934.
12. Blalock, A., Cunningham, R. S., and Robinson, C. S.: Experimental Production of Chylothorax by Occlusion of the Superior Vena Cava, *Ann. Surg.* 104: 359, 1936.
13. Wagner, K.: Symptomatology of Stenosis with Occlusion of the Lumen of the Superior Vena Cava, *Polska gaz. lek.* 11: 61 and 81, 1932.
14. Lian, C., and Abaza, A.: Dissociation de la Pression veineuse et de la Vitesse Circulatoire Signe Caracteristique de l'Obstruction de la Veine Cave Supérieure. *Bull. et mém. Soc. méd. d. hôp. de Paris* 51: 730, 1935.

THE COLD-PRESSOR REACTION IN NORMAL SUBJECTS AND IN PATIENTS WITH PRIMARY (ESSENTIAL) AND SECONDARY (RENAL) HYPERTENSION*

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SINCE 1932, when Hines and Brown¹ first reported the response of blood pressure to a standard stimulus of cold, this reaction has been studied by numerous investigators. The results, as indicated in a recent critical review of the literature by Ayman and Goldshine,² have not been uniform. The reasons for the discrepancies have been discussed adequately by these writers. In this communication, therefore, the literature on this subject will not be reviewed in detail.

Our interest in this problem was to determine whether the cold-pressor reaction could be used to differentiate between essential hypertension and the secondary forms of hypertension, particularly the type seen in chronic renal disease. For the purpose of evaluating these results statistically, a group of normal subjects was also studied.

METHOD AND MATERIAL.

With the exception that we used a recording sphygmomanometer, the method employed was that described by Hines and Brown.¹ The test was carried out with the subject in a comfortable sitting position, except in a few instances in which the patients were recumbent in bed. The blood pressure cuff was applied to one arm, and the other arm was left free. Blood pressure readings were then taken at frequent intervals until a uniform control level was reached. Because of the mechanical slowness of the recording sphygmomanometer, blood pressure readings could not be made at exactly 30- and 60-second intervals after immersion of the hand in water at from 4 to 5° C. In order to keep within the minute limit, therefore, recordings of the blood pressure were taken as rapidly as possible (at least two being obtained), and were discontinued after the hand had been submerged in ice water approximately one minute. Blood pressure recordings were then continued after the hand had been removed from the ice water until the blood pressure had returned to the control level; the time required for the return to the original level was noted.

Eighty-nine subjects were studied; twenty-six were considered as normal individuals, and consisted of interns, laboratory workers, and other members of the usual hospital staff. Eleven subjects had chronic renal disease with or without hypertension, and fifty-two subjects were classified as having essential hypertension.

Following the classification of Hines and Brown, the normal group was divided into two categories, namely, (a) those having a rise of less than 22 mm. Hg systolic and diastolic (16 subjects), who will henceforth be referred to as normals, and (b) those having a rise in systolic or diastolic blood pressure greater than 22 mm. Hg (10 subjects), henceforth referred to as hyperreactor normals.

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Received for publication April 10, 1939.

RESULTS

Table I gives a comprehensive picture, including a statistical analysis, of the results obtained. In the group of sixteen normal subjects, the average age was 28 years; five were females. The mean rise in blood pressure was 13.9 ± 4.4 mm. Hg, systolic, and 11.8 ± 4.4 mm. Hg, diastolic. In the ten hyperreactor normal subjects, the average age was 27 years; two were females. The mean rise in blood pressure was 37.4 ± 9.2 mm. Hg, systolic, and 25.3 ± 9.1 mm. Hg, diastolic.

Of the eleven subjects with chronic renal disease, the average age was 36 years; four were females. The mean rise in blood pressure was 16.5 ± 7.8 mm. Hg, systolic, and 12.6 ± 6.5 mm. Hg, diastolic.

Of the fifty-two subjects with essential hypertension, the average age was 54 years; thirty-three of the group were females. The mean rise in blood pressure in response to the standard cold stimulus was 35.0 ± 20.0 mm. Hg, systolic, and 21.7 ± 12.2 mm. Hg, diastolic.

Table I also shows that the responses both of the hyperreactor normal subjects and the patients with essential hypertension deviate sufficiently from the normal to be statistically significant. The lack of any appreciable variation from normal in the blood pressure response of patients with nephritis is also evident.

Since only 76 per cent of the patients with essential hypertension gave a hyperreactor response to a standard cold stimulus, an attempt was made to ascertain what factors might influence the degree of pressor reaction in these patients. Thus, as indicated in Table I, the patients with essential hypertension were subdivided into smaller groups according to degree of arteriosclerosis, presence or absence of albuminuria, duration of hypertension, and, finally, according to age. It will be observed that those individuals exhibiting moderate to severe degrees of arteriosclerosis, those having albuminuria (a secondary manifestation in these patients, due to nephrosclerosis), and the aged (61 to 75 years) had an appreciably smaller pressor response to cold than those patients who manifested few or none of these complications, or were younger. However, a considerable number of the older patients with arteriosclerosis gave a hyperreactor response to cold; apparently these factors alone do not account for the lack of a hyperreactor response in some patients with essential hypertension. The duration of the hypertension exerted little or no influence on the degree of pressor response in these patients. This confirms the clinical impression that the duration of hypertension, in general, bears little or no relation to the severity or extent of the secondary lesions.

It was pointed out above that the technique used in this study was fundamentally that employed by Hines and Brown,¹ and later by Ayman and Goldshine.² For this reason our results have been compared with theirs (Table II) and show a close agreement.

TABLE I
A STATISTICAL ANALYSIS OF THE RESPONSE OF BLOOD PRESSURE TO A STANDARD COLD STIMULUS IN 89 SUBJECTS

GROUP	NO. OF SUB- JECTS	NO. OF TESTS	AVER- AGE AGE IN YEARS	SEX		AVERAGE BLOOD PRESSURE		ARITHMETIC MEAN OF RISE IN BLOOD PRESSURE		STANDARD DEVIATION*		PROBABLE ERROR OF MEAN†		d \pm σ_d
				M.	F.	SYSTOLIC	DIASTOLIC	SYSTOLIC	DIASTOLIC	SYSTOLIC	DIASTOLIC	SYSTOLIC	DIASTOLIC	
Normal	16	17	28	11	5	123	77	13.0	11.8	± 4.4	± 4.1	0.72	0.72	0
Hyperreactor Normal	10	12	27	8	2	129	80	37.4	25.3	± 9.2	± 9.1	1.79	1.77	8.22
Nephritic Hypertension	11	16	36	7	4	163	94	16.5	12.6	± 7.8	± 6.5	1.32	1.10	1.17
Essential Hypertension	52	58	54	19	33	209	113	35.0	21.7	± 20.0	± 12.2	1.73	1.08	7.45
A. Arteriosclerosis 0 to +	35	37	50	11	24	201	108	38.9	22.8	± 21.1	± 13.0	2.34	1.44	6.91
Arteriosclerosis ++ to + + + +	17	21	60	8	9	223	122	28.1	19.8	± 15.9	± 11.6	2.34	1.71	3.92
B. Albuminuria 0	35	37	39	12	23	200	108	37.1	22.1	± 22.3	± 13.2	2.47	1.46	5.47
Albuminuria + to + + +	13	17	55	7	6	230	129	30.5	21.8	± 17.0	± 11.1	2.78	1.82	3.91
C. Duration less than 5 years	20	20	54	6	14	206	107	31.1	20.5	± 19.1	± 13.0	2.88	1.96	3.91
Duration more than 5 years	18	21	53	6	12	221	120	33.7	20.0	± 22.0	± 9.1	3.24	1.31	4.03
D. Age 30 to 50 years	18	22	45	4	14	203	118	35.5	20.7	± 25.6	± 12.9	3.68	1.86	4.32
Age 51 to 60 years	23	25	55	9	14	215	114	38.0	23.5	± 19.3	± 12.1	2.60	1.63	6.95
Age 61 to 75 years	10	10	68	4	6	213	106	28.4	20.1	± 12.8	± 13.2	2.73	2.82	3.47

Standard Deviation: $\sigma = \sqrt{\frac{\sum (d^2)}{N}}$.Where $\sum (d^2)$ represents the summation of the squares of the individual deviations from the mean, and N the number of determinations.†Probable Error of Mean = $0.6745 \frac{\sigma}{\sqrt{N}}$.Where σ represents the standard deviation, and N the number of determinations. $\frac{d}{\sigma_d}$ represents the difference between two means divided by the standard error of the difference. The standard error of the difference σ_d is calculated from the formula, $\sigma_d = \sqrt{\frac{\sigma_1^2}{N_1} + \frac{\sigma_2^2}{N_2}}$.Where σ_1 and σ_2 represent the standard deviations of the two groups and N_1 and N_2 represent the number of determinations in the two groups.

TABLE II

A COMPARISON OF OUR OBSERVATIONS WITH THOSE OF PREVIOUS WORKERS ON THE MEAN RISE OF BLOOD PRESSURE PRODUCED BY A STANDARD COLD STIMULUS

GROUP	HINES AND BROWN		AYMAN AND GOLDSHINE		PRESENT REPORT	
	SYSTOLIC	DIASTOLIC	SYSTOLIC	DIASTOLIC	SYSTOLIC	DIASTOLIC
Normal	11.4	10.6	10.5	9.0	13.9	11.8
Hyperreactor Normal	29.4	24.5	33.0	17.8	37.4	25.3
Nephritis with and without Hypertension					16.5	12.6
Essential Hypertension						
Preorganic	47.2	34.3				
Organic	34.4	25.4				
All Cases			33.5	19.0	35.0	21.7

DISCUSSION

As stated at the outset, our prime interest in this problem was to determine whether or not the cold-pressor test could be used to differentiate between essential hypertension and hypertension due to chronic renal disease. During the course of this work, Alam and Smirk³ reported their studies on this subject, showing that, unlike most patients with essential hypertension, patients with nephritic hypertension do not exhibit a pressor response to cold. Our results are in agreement with theirs. Our patients with renal hypertension, however, had an average rise, in both systolic and diastolic blood pressure, slightly higher than in normal subjects, whereas those of Alam and Smirk gave a lower response.

No specific mention was made above of the time required for the blood pressure to return to the control level after removal of the hand from the ice water. Our observations in this respect agree with those of previous writers. Whereas the blood pressure returns to the control level in approximately one minute in normal subjects, this interval may be prolonged to from two to ten minutes in hyperreactor normals and in patients with essential hypertension. Patients with nephritic hypertension are similar to normal subjects in this respect.

SUMMARY

The blood pressure responses to a standard cold stimulus, using a recording sphygmomanometer, in a group of 89 persons, comprising normal subjects, hyperreactor normal subjects, patients with nephritis with and without hypertension, and patients with essential hypertension, are reported and studied statistically.

Thirty-nine per cent of the normal subjects and 76 per cent of the patients with essential hypertension gave a hyperreactor response to cold.

The influence on the cold-pressor reaction of such factors as arteriosclerosis, albuminuria, duration of hypertension, and age of the patients with essential hypertension is discussed.

The blood pressure response to cold in patients with chronic nephritis is similar to that of normal subjects who are not hyperreactors. A hyperreactor response, therefore, in a patient with increased arterial pressure would exclude the possibility of hypertension due to chronic renal disease, but the converse is not true.

Grateful recognition is given to Dr. Robert T. Garrett, of Southampton, Long Island, N. Y., for his aid during the earlier part of these experiments.

REFERENCES

1. Hines, E. A., Jr., and Brown, G. E.: Standard Stimulus for Measuring Vasomotor Reactions, *Proc. Staff Meet. Mayo Clin.* 7: 332, 1932.
2. Ayman, D., and Goldshine, A. D.: Cold as a Standard Stimulus of Blood Pressure, *New England J. Med.* 17: 650, 1938.
3. Alam, M., and Smirk, F. H.: Blood Pressure Raising Reflexes in Health, Essential Hypertension and Renal Hypertension, *Clin. Sc.* 3: 259, 1938.

THE CLINICAL SIGNIFICANCE OF RIGHT AXIS DEVIATION IN THE ELECTROCARDIOGRAM

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IN SPITE of the crudeness of the estimation of the electrical axis of the heart by means of the electrocardiogram, significant deviations from the usual normal limits have a clinical value which is not sufficiently appreciated. The scarcity of practical information in the literature concerning the limits of the normal electrical axis and the meaning of abnormal degrees of axis deviation is surprising to those of us who are engaged in clinical electrocardiography. This applies particularly to right axis deviation, about which there exists no adequate clinical study, so far as we are aware.* The purpose of this report is to supply this need and thereby to increase the accuracy of differential diagnosis.

MATERIAL

The basis of this report consists of electrocardiograms of 200 individuals, aged 5 years, or more, showing right axis deviation of more than $+90^\circ$ without low voltage or bundle branch block, but unselected in so far as the clinical diagnosis was concerned. These 200 cases were found among the records of approximately 6000 ($3\% \pm$) individuals who had had electrocardiograms at the Massachusetts General Hospital. The electrical axis was estimated in degrees by the graphic method to be referred to below, i.e., Einthoven's triangle, as presented by Carter, Richter, and Greene.² All tracings having low voltage (maximum height of the QRS complex 5 millivolts, or less) in the standard leads were eliminated because of the unreliability of axis determinations in such instances. Electrocardiograms showing bundle branch, i.e., intraventricular, block were also excluded. Because of the natural tendency to right axis deviation in infants and young children, no patient under 5 years of age was included in this study, and all but five patients were over 10 years of age. Each case record was carefully reviewed, and if there was any doubt as to the cardiac diagnosis, the case was excluded.

As an adjunct to the above material it seemed worth while to evaluate right axis deviation in regard to cor pulmonale, and to the three most common types of congenital heart disease, i.e., the tetralogy of Fallot, interventricular septal defect, and patent ductus arteriosus. Consequently, the electrical axis was estimated in a separate group of such cases if the clinical diagnosis seemed unquestionable.

GENERAL CONSIDERATIONS

At the outset it should be realized that the determination of the electrical axis of the heart by the electrocardiogram is, at best, only a rough

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Received for publication May 8, 1939.

*Recently Mola¹ has published a detailed study of the electrocardiographic types of right axis deviation in 128 patients, but his paper does not concern itself with the clinical significance of right axis deviation in general.

measurement. This is so because the classical electrocardiogram records the differences in potential produced by the contracting heart muscle in one plane only, whereas actually, since the heart is a solid body, these electrical forces are taking place in many different planes. It is not our purpose to discuss the electrophysical and mathematical concepts upon which the determination of the electrical axis of the heart by the electrocardiogram is based. A review of this material can be found in the report by Prodger and Davis.³ A summary of the existing factual data and theoretical concepts in so far as they apply to the practical aspects of axis deviation, however, is desirable as a background for the material to be presented subsequently.

The electrical axis as determined by the electrocardiogram can be expressed in one of two ways, either in terms of an angle with the horizontal, or by means of an index. The former was originally suggested by Einthoven, and later simplified for practical application by Carter, Richter, and Greene² to a graphic method based on Einthoven's equilateral triangle. Formulas for expressing the electrical axis in terms of an index have been presented by Lewis⁴ and White and Bock.⁵ There is some difference of opinion regarding the normal limits of the electrical axis. When the angle is employed, both 0° and -10° on the one hand, and $+90^\circ$ and $+100^\circ$ on the other, have been considered the upper boundaries for left and right axis deviation, respectively. With the index, values more positive than +20 or more negative than -10 are usually considered as indicative of abnormal left and right axis deviation, respectively. The index is perhaps slightly more reliable for estimating significant left axis deviation, while the angle seems to express right axis deviation more satisfactorily. Both methods, however, are arbitrary, neither is wholly reliable, and comparison of the two indicates that they are about equally satisfactory clinically.

The reliability of axis deviation in the electrocardiogram as a method of estimating relative ventricular strain has been tested in the past: by comparing the axis deviation with (1) the relative post-mortem weights of the two ventricles, (2) the relative ventricular strain to be expected with the type of heart disease as diagnosed clinically, and (3) the relative size of each ventricle as shown by roentgenographic examination. The number of these studies is few, and the importance to be attached to them is in the order mentioned above. The difficulty of ascertaining the ratio of enlargement of the ventricles roentgenologically, except when they are very abnormal, is familiar to anyone experienced with cardiac roentgenography. On the other hand there is also difficulty in relying on current autopsy data, since ventricular volumes, as well as weights, undoubtedly should be taken into consideration.

There exist only three reports based on anatomic studies. Lewis⁴ and Cotton⁶ compared axis deviation and the relative ventricular weights in

15 hearts and came to the conclusion that axis deviation as estimated by electrocardiography was a reliable method of detecting ventricular preponderance, especially of the right ventricle. Later, Herrmann and Wilson,⁷ as a result of similar studies on 59 hearts, questioned the validity of such a conclusion except in those cases in which considerable cardiac enlargement existed. The discrepancy in these results apparently rests upon the fact that both Lewis and Cotton used only cases in which there was marked cardiac enlargement.

The conclusions of Herrmann and Wilson are worthy of mention and have been summarized as follows:

1. The relative weight of the two ventricles is but one of many factors which influence the form of the ventricular complex of the electrocardiogram. Its influence predominates only when the heart is greatly hypertrophied. There is no definite relation between the form of the ventricular complex and the relative weight of the two ventricles when the ventricular weight is below 250 gm.

2. The chief factors which disturb the relation between the form of the electrocardiogram and the relative weight of the two ventricles, so it is suggested, are: (1) variations in the position of the heart, (2) variations in the arrangement of the ventricular conducting system, and (3) disturbances of intraventricular conduction.

3. The form of the normal electrocardiogram is not determined by the relative weight of the two ventricles; it is chiefly dependent upon the position of the heart and upon the arrangement of the ventricular conducting system; sometimes one, sometimes the other, of these factors exerts the greater influence.

Just how much importance is to be placed on differences in the architecture of the conduction system and differences in the rate of intraventricular conduction (excluding degrees which give bundle branch intraventricular block) is difficult to ascertain at present. Such concepts are still based largely on theoretical grounds.

The importance of the position of the heart with respect to axis deviation, however, is recognized clinically and has been firmly established experimentally. It is well known that the heart of the asthenic individual is usually vertically placed in the chest and that when this is the case there is a tendency for the electrical axis to deviate to the right, whereas the obese or stocky individual usually has a transverse heart with a tendency to left axis deviation. Further, it is true that roentgenographic examination of the vertical heart in the anterior position not infrequently shows slight fullness or prominence in the region of the pulmonary conus. This can be explained anatomically by slight rotation of the heart to the left around its long axis, bringing into relief the conus pulmonalis and the base of the pulmonary artery. The relationship between the position of the heart and the electrical axis has been studied experimentally both by theoretical rotation of the human

heart,^{8, 9} which can be approximated by varying the position of the electrocardiographic leads, and by actual displacement experiments in animals.^{10, 11} It is generally agreed that displacement to the right or left alone causes no significant alterations in the electrical axis, but that rotation of the heart, particularly about its longitudinal axis, does produce significant axis deviation. Rotation to the left about the longitudinal axis produces right axis deviation, while a reverse rotation causes the axis to deviate to the left. Meek and Wilson,¹¹ by correlating the anatomical studies of Groedel and Mönckeberg¹² and their own rotation experiments, bring out the significant point that the changes in the anatomical relationships of the ventricles and septum which occur when there is hypertrophy of the right or left chamber are duplicated by rotation of the heart about the longitudinal axis. There seems little doubt, then, that the position of the heart in the chest, or, perhaps better, the relative position of the ventricles and septum in the thoracic cage, is of primary importance in determining the position of the electrical axis of the heart.

Clinical studies^{13, 3, 5, 14} have shown, as a rule, a correlation between the ventricular preponderance expected in a given type of heart disease and the axis deviation. Progger and Davis³ have shown by roentgenographic studies that the correlation between axis deviation and type of heart disease is closer in enlarged hearts than in hearts of normal size. This adds clinical support to the conclusions of Herrmann and Wilson.⁷ Although there are no specific studies to substantiate the following, it seems certain that the degree and duration of the heart disease and neutralizing valvular lesions, in so far as they effect relative ventricular hypertrophy, are important factors in determining the degree of axis deviation. In this regard Thompson and White¹⁵ have shown that in heart disease affecting primarily the left ventricle, particularly when there has been chronic left ventricular failure, there is commonly right ventricular hypertrophy which sometimes counterbalances, in part or wholly, the left axis deviation, and in a rare case is sufficient even to produce significant right axis deviation.

DISCUSSION OF PRESENT STUDY

An analysis by ourselves of the relative frequency of right and left axis deviation in 15,000 electrocardiograms showed that significant left axis deviation was approximately five times as frequent as significant right axis deviation.* This ratio undoubtedly would favor the former even more in those regions where rheumatic heart disease is not so prevalent as in New England. In our series, for example, rheumatic heart disease accounted for almost half (45.5 per cent) of the entire number of cases of right axis deviation.

*Left axis deviation occurred 2,654 times, while right axis deviation was found in 516 cases.

TABLE I
DISTRIBUTION OF 200 UNSELECTED CASES OF RIGHT AXIS DEVIATION

CLINICAL STATUS	RIGHT AXIS DEVIATION (IN DEGREES, USING EINTHOVEN'S TRIANGLE)										TOTAL
	+90° TO +94°	+95° TO +99°	+100° TO +104°	+105° TO +109°	+110° TO +114°	+115° TO +119°	+120° TO +129°	+130° +			
Normal Hearts	15	26	21	10	2	1	0	0		75 (37.5%)	
Mitral Stenosis Without Aortic Regurgitation	11	7	15	10	9	5	2	4		63 (31.5%)	
Mitral Stenosis With Aortic Regurgitation	4	2	7	2	6	3	2	0		26 (13%)	
Congenital Heart Disease	0	1	1	2	0	2	2	6		14 (7%)	
Coronary Heart Disease	1	1	3	1	0	0	0	1		7 (3.5%)	
Cor Pulmonale	2	1	0	0	0	1	0	1		5 (2.5%)	
Miscellaneous *	3	4	0	2	0	0	0	1		10 (5%)	
Total	36 (18%)	42 (21%)	47 (23.5%)	27 (13.5%)	17 (8.5%)	12 (6%)	6 (3%)	13 (6.5%)		200 (100%)	

*Lupus erythematosus disseminatus with cardiac involvement, 2 cases; chronic constrictive pericarditis, 2 cases; acute glomerular nephritis with inverted T waves in Leads I, II, and IV, 1 case; chronic glomerular nephritis with pericarditis and inverted T waves in Leads I and IV, 1 case; thyrotoxicosis, 1 case; rheumatic heart disease with mitral regurgitation, 1 case, with slight aortic regurgitation, 1 case; and heart disease of undetermined etiology (: cor pulmonale), 1 case.

The distribution of our series of 200 cases of right axis deviation in respect to the degree of axis deviation and the clinical condition of the heart (Table I) brings out several significant points. It is interesting that almost as many patients with right axis deviation revealed no heart disease (37.5 per cent) as showed mitral stenosis (44.5 per cent). Also, it is important to note that the degree of axis deviation which occurs normally exceeds the commonly accepted upper normal limits. Furthermore, it is evident that right axis deviation of more than $+109^\circ$ is very rarely found normally; therefore, one is justified in considering an axis deviation of $+110^\circ$ or more as definite evidence of organic heart disease.

Right axis deviation without low voltage or wide QRS waves occurred in only seven cases of coronary heart disease, and even then, in only one case (autopsy) was the axis deviation of more than slight degree. In this case there was no post-mortem evidence of right ventricular strain, and the right axis deviation was in all probability due to the position of the heart. We believe that in most instances of coronary heart disease right axis deviation is to be explained on this basis. The infrequency of right axis deviation with coronary heart disease is particularly significant, since in this clinic the number of electrocardiograms taken on individuals with this type of heart disease is large. Despite the unquestionably high incidence of coronary heart disease among the 6000 individuals, there were only 7 such cases in which there was right axis deviation. One must conclude, therefore, that the finding of right axis deviation in the electrocardiogram is strong evidence that the patient does not have coronary heart disease, and, consequently, every other etiologic possibility should be excluded before such a diagnosis is made when right axis deviation is present. In our series of 200 instances of right axis deviation there were 2 cases in which coronary heart disease was diagnosed clinically, in both of which cor pulmonale was found at autopsy.

As might be expected, patients with congenital heart disease showed the greatest proportion of high degrees of right axis deviation, while those with mitral stenosis without aortic regurgitation, and with aortic regurgitation, followed in that order. One should recognize the fact that in aortic regurgitation, when there is a mid-diastolic murmur, and the question arises whether this murmur is functional (Austin Flint) or due to mitral stenosis, considerable left axis deviation favors the former, whereas no axis deviation or slight right axis deviation favors the latter.

The age distribution in these cases (Table II) is consistent with that which is to be expected from the etiology of the heart disease. The diminution in the number of subjects with normal hearts after middle age is probably to be attributed to two factors, first, the increase in the amount of coronary heart disease, either clinical or electrocardiographic, and, second, the tendency at this age for the body weight to increase,

which would cause the electrical axis of the heart to rotate toward the left, counterbalancing any pre-existing right axis deviation and in some individuals even producing some left axis deviation.

TABLE II

DISTRIBUTION OF 200 CASES OF RIGHT AXIS DEVIATION WITH RESPECT TO AGE AND CARDIAC STATUS IN INDIVIDUALS OVER 5 YEARS OF AGE

AGE	CARDIAC STATUS						TOTAL NUMBER OF CASES
	NORMAL HEARTS	RHEU- MATIC HEART DISEASE	CORO- NARY HEART DISEASE	CON- GENITAL HEART DISEASE	COR PULMONALE	MISCEL- LANEOUS	
5 to 9 yr.	1	3	0	1	0	0	5 (2.5%)
10 to 19 yr.	13	20	0	9	0	1	43 (21.5%)
20 to 29 yr.	30	20	0	2	0	5	57 (28.5%)
30 to 39 yr.	16	31	1	1	0	0	49 (24.5%)
40 to 49 yr.	9	12	2	1	1	0	25 (12.5%)
50 to 59 yr.	3	4	2	0	1	2	12 (6.0%)
60 to 69 yr.	2	0	1	0	2	0	5 (2.5%)
70 to 79 yr.	1	1	1	0	1	0	4 (2%)

The significant conclusions suggested by Table III may be summarized as follows: (1) the tetralogy of Fallot always causes right axis deviation,* usually of a high degree; (2) an interventricular septal defect rarely causes any deviation of the electrical axis, and, if it does, the tendency is for right axis deviation to occur; (3) patency of the ductus arteriosus almost never causes right axis deviation, but may cause significant left axis deviation; and (4) in cor pulmonale there is always right axis deviation (or a tendency to right axis deviation), although not necessarily of a high degree.

In conclusion, we wish to emphasize that axis deviation, and particularly right axis deviation, has a practical value which frequently is not appreciated. The significance of even a slight degree of right axis deviation should not be overlooked, since its proper evaluation may be of prime importance in leading to a correct clinical diagnosis. We believe that it is a wise rule to explain right axis deviation adequately in every instance. In persons with normal hearts, a vertical position of the heart in the chest or its rotation around its longitudinal axis toward the left by a thoracic or spinal deformity is the most important factor leading to right axis deviation, while in subjects with transverse or enlarged hearts, right axis deviation is almost always due to a cardiac defect which has led, either primarily or secondarily, to right ventricular strain. The effects of position and of disease may be combined in the same case.

SUMMARY

1. We have made a clinical analysis of 200 cases in which the electrocardiogram showed right axis deviation of more than $+90^\circ$, excluding

*In very rare cases of the tetralogy of Fallot there is also a congenital dextrocardia which inverts Lead I and so neutralizes the right axis deviation.

TABLE III

TYPE OF HEART DISEASE	NUMBER OF CASES	LEFT AXIS DEVIATION	NO AXIS DEVIATION	RIGHT AXIS DEVIATION						RIGHT BUNDLE BRANCH BLOCK
				+90° TO +99°	+100° TO +109°	+110° TO +119°	+120° TO +129°	+130°+	LOW VOLTAGE	
Tetralogy of Fallot	15	0	0	0	1	1	2	10	0	1
Interventricular Septal Defect	14	0	11	0	1	1	0	0	0	1
Patent Ductus Arteriosus	17	4 (-7° to -10°)	11	1	1	0	0	0	0	0
Cor Pulmonale	9	0	0	3	1	2	0	2	1	0
	6	0	0	1	0	2	1	2	0	0

those with low voltage of the QRS complexes and intraventricular or bundle branch block. The most common findings were mitral stenosis, in 44.5 per cent of the cases, and no heart disease, in 37.5 per cent, leaving only 18 per cent associated with other conditions. Congenital heart disease was the third most common finding, responsible for 7 per cent of the cases.

2. The upper normal limit of right axis deviation we found to be -109° , except for 3 cases. We believe, therefore, that axis deviation of $+110^\circ$, or more, practically always indicates organic heart disease.

3. Of the 200 cases of right axis deviation, coronary heart disease was found in only 7 (3.5 per cent), and in only one was it of more than slight degree. The position of the heart in the chest, rather than right ventricular strain, probably accounts for this combination. In view of the fact that the incidence of coronary heart disease is high among patients whose electrocardiograms are made in this laboratory, it is evident that the finding of right axis deviation electrocardiographically is strong, though not conclusive, evidence that the patient does not have coronary heart disease. In such cases cor pulmonale, particularly, should be considered.

4. An analysis of the electrocardiogram with regard to axis deviation in cases of cor pulmonale and of the most common types of congenital cardiac defects (tetralogy of Fallot, interventricular septal defect, and patent ductus arteriosus) led to the following conclusions: (1) the tetralogy of Fallot always causes right axis deviation, usually of a high degree, except when there is an associated congenital dextrocardia; (2) interventricular septal defect rarely causes any deviation of the electrical axis, and if it does, the tendency is for right axis deviation to occur; (3) patency of the ductus arteriosus almost never causes right axis deviation, but may cause significant left axis deviation; and (4) in cor pulmonale there is always right axis deviation (or a tendency to right axis deviation), although not necessarily of high degree.

5. We believe that even a slight degree of right axis deviation may be very significant and that its proper evaluation can be of prime importance in leading to a correct clinical diagnosis. In the normal person a vertical position of the heart in the chest or its rotation to the left around its longitudinal axis by a thoracic or spinal deformity is the most important factor leading to right axis deviation; while in the case of a transverse or enlarged heart, right axis deviation is almost always due to a cardiac defect which has led, either primarily or secondarily, to right ventricular strain.

REFERENCES

1. Moia, B.: Un estudio del complejo ventricular en los E.C.G. con desviacion del eje electrico a la derecha. *Rev. argent. de cardiol.* 5: 221, 1938.

2. Carter, E. P., Richter, C. P., and Greene, C. H.: A Graphic Application of the Principle of the Equilateral Triangle for Determining the Direction of the Heart in the Human Electrocardiogram, *Bull. Johns Hopkins Hosp.* 30: 162, 1919.
3. Prodiger, S. H., and Davis, D.: The Significance of Axis Deviation in the Human Electrocardiogram, *Arch. Int. Med.* 45: 974, 1930.
4. Lewis, T.: Observations on Ventricular Hypertrophy With Especial Reference to Preponderance of One or Other Chamber, *Heart* 5: 367, 1913.
5. White, P. D., and Beck, A. V.: Electrocardiographic Evidence of Abnormal Ventricular Preponderance and of Auricular Hypertrophy, *Am. J. M. Sc.* 156: 17, 1918.
6. Cotton, T. F.: Observations on Hypertrophy, *Heart* 6: 217, 1915.
7. Herrmann, G. R., and Wilson, F. N.: Ventricular Hypertrophy: A Comparison of Electrocardiographic and Post-Mortem Observation, *Heart* 9: 94, 1922.
8. Cohn, A. E., and Raisbeck, M. J.: An Investigation of the Relation of the Position of the Heart to the Electrocardiogram, *Heart* 9: 312, 1921-22.
9. Cohn, A. E., and Raisbeck, M. J.: On the Relation of the Position of the Enlarged Heart to the Electrocardiogram, *Heart* 9: 334, 1921-22.
10. Kountz, W. B., Prinzmetal, M., and Smith, J. R.: The Effect of Position of the Heart in the Electrocardiogram. III. Observations Upon the Electrocardiogram of the Monkey, *AM. HEART J.* 10: 623, 1931-35.
11. Meek, W. J., and Wilson, A.: The Effect of Changes in Position of the Heart on the QRS Complex of the Electrocardiogram, *Arch. Int. Med.* 36: 614, 1925.
12. Groedel, T., and Mönchberg, J. G.: Ein Fall von longitudinaler Pulmonalstenose und die sich daraus ergebenden Schlüsse für die Initial-Ziele des Elektrocardiogramms, *Zentralbl. f. Herz- u. Gefässerkr.* 5: 2, 1913.
13. Carter, E. P., and Greene, C. H.: The Electrocardiogram and Ventricular Preponderance, *Arch. Int. Med.* 24: 678, 1919.
14. White, P. D., and Burwell, C. S.: The Effects of Mitral Stenosis, Pulmonary Stenosis, Aortic Regurgitation, and Hypertension on the Electrocardiogram, *Arch. Int. Med.* 34: 529, 1924.
15. Thompson, W. P., and White, P. D.: The Commonest Cause of Hypertrophy of the Right Ventricle—Left Ventricular Strain and Failure, *Am. Heart J.* 12: 644, 1936.

THE PRECORDIAL ELECTROCARDIOGRAM IN MYOCARDIAL INFARCTION

II. OBSERVATIONS ON CASES OF INFARCTION OF THE POSTERIOR WALL OF THE LEFT VENTRICLE

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THE purpose of this second article of a series is to describe the potential variations of the extremities and of the precordium^{1,2} in two cases of infarction limited to the posterior portions of the left ventricle. The methods of study employed have been considered in Part I.³ For reasons beyond our control the heart in Case 5 could not be grossly sectioned by the method devised by one of us (C. E. C.). It was otherwise examined as previously described. Standard and special electrocardiograms in Case 6 were recorded simultaneously with Lead I, and the time between the beginning of QRS in this lead and the intrinsicoid⁴ deflection measured. Since these have no relation to the problem under consideration they are to be disregarded.

REPORT OF CASES

CASE 5.—B. G., a 65-year-old white woman, knew that she had had hypertension for three years and diabetes mellitus for one year prior to admission. She had no cardiac symptoms until Sept. 29, 1936, when weakness and vague pains in the chest appeared. The following evening, and again on the morning of Oct. 1, she vomited about a pint of dark red blood. After the second hematemesis she was admitted to the hospital, conscious, but showing evidences of recent blood loss, namely, cold, clammy skin, ventricular and pulse rates of 120 per minute, and a blood pressure of 86/56. The rectal temperature was 98.8° F. The heart sounds were distant. Numerous premature systoles occurred paroxysmally. Abdominal examination was negative on admission. There was no evidence of congestive heart failure.

During her two weeks in the hospital nine blood examinations showed that the average number of erythrocytes was 3.0 million and that the average hemoglobin value was 10 gm. The leucocytes ranged from 13,500 to 24,250, with polymorphonuclear leucocytes varying from 83 to 93 per cent. The urine contained protein (2 plus), and occasionally a trace of sugar. The blood sugar content, determined twice, was 267 mg. per cent. The nonprotein nitrogen content of the blood was 100, 128, and 64 mg. per cent on three different occasions. At first the stools were tarry and gave a positive reaction with benzidine. Two cultures of the blood showed no growth after five days. The blood Wassermann reaction was negative. The mean blood pressure for two weeks (daily readings) was 125/68.

Therapy directed toward replacement of blood loss caused temporary improvement and a rise in blood pressure. On Oct. 5 the patient became restless and complained of discomfort under the lower portion of the sternum. For the first time, a tender, globular mass was palpated in the right upper quadrant of the abdomen. Long periods of stupor, with brief remissions, ensued. A sharp rise in

Received for publication May 25, 1939.

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rectal temperature, to 105° F., followed each of two direct transfusions of 300 c.c. of blood, given Oct. 6 and Oct. 8. Toward the end a bilateral suppurative parotitis developed. Rales in the bases of the lungs and pretibial edema were observed during the patient's stay in the hospital, but the edema disappeared before death, which occurred Oct. 14, 1936.

It could not be determined when occlusion of a coronary artery occurred, but from a consideration of the available facts and electrocardiograms, it appeared to have been some time between Sept. 29 and Oct. 5, 1936.

Necropsy.—The heart weighed 320 gm. The mitral and aortic valves were thickened, and the mitral annulus calcified. The wall of the left ventricle measured 15 to 17 mm. in thickness in most locations. The endocardium was smooth throughout but was discolored in an area about 3 cm. in diameter on the posterior wall of the left ventricle behind the posterior leaflet of the mitral valve. This area also included the posterior portion of the interventricular septum and extended as high as the mitral annulus. The discolored myocardium under it extended to the epicardium, and was 6 to 8 mm. thinner than other parts of the wall. Microscopic examination showed that it consisted of necrotic myocardium with young connective tissue at its margins. The remainder of the left ventricle contained microscopic areas of focal fibrosis.

The left coronary artery was patent at its origin. In the ramus descendens anterior were several eccentric plaques, some of them calcified, which reduced the lumen to less than one-third of normal at points 3 cm. and 7 cm. from its origin. The left circumflex was a small, though thin-walled, vessel. The right coronary showed eccentric intimal swellings throughout. Six cm. from its origin hyalinized intimal connective tissue made considerable encroachment on the lumen, and in the next centimeter of the vessel's extent the lumen was occluded by a fresh, organizing thrombus. Beyond the thrombus no gross or microscopic disease was found.

Electrocardiograms.—Four standard electrocardiograms were recorded between Oct. 5 and Oct. 10. The first of these showed the typical Q_sT_s contour usually associated with recent infarction of the posterior wall of the left ventricle (Fig. 1). There were a deep Q wave in Leads II and III, low amplitude of the initial ventricular deflections in Lead II, a depressed RS-T segment in Lead I, and an elevated RS-T segment in Leads II and III. The P-R interval was 0.24 second in the first curve, and 0.16 second, or less, in subsequent ones. The last electrocardiogram taken showed less of the earlier RS-T displacement, and a considerable diminution in amplitude of all deflections. Auricular, blocked auricular, and ventricular premature systoles, and shifting of the pacemaker within the sinoauricular node were present in the earlier curves.

The extremity and precordial potentials (Fig. 1) were taken Oct. 7, 1936. In the former, the deep Q wave in Lead V_F was the only abnormality. Slight reciprocal displacement of the RS-T segment in Leads V_L and V_R was noted. The precordial potentials were recorded with the string sensitivity at seven-tenths normal (1 mv. = 0.7 cm.). There were no abnormalities of the initial ventricular deflections. The T wave in Leads V_2 , V_3 , and V_4 was abnormal.

CASE 6.—A 53-year-old white man was admitted to the hospital on four different occasions. The first was in November, 1933, because of the sudden onset of paresis of the extremities, loss of speech, incontinence of urine, and stupor. These symptoms disappeared after forty-eight hours. Clinical and laboratory study revealed hypertensive neuroretinopathy, proteinuria, anemia, a blood non-protein nitrogen content of 45 to 50 mg. per cent on various occasions, and a mean blood pressure of 163/89 over a period of two weeks. The fasting blood sugar value was 215 mg. per cent, and on one occasion glycosuria was present. The Wassermann reaction on the spinal fluid was weakly positive (1 plus), and on the blood, negative.

On Dec. 25, 1933, the patient had a sudden attack of dyspnea. He was readmitted to the hospital three weeks later because of complaints referable to diminished cardiac reserve. The heart sounds were distant and a systolic murmur was heard at the apex. A teleroentgenogram showed enlargement of the heart and dilatation of the aorta. The mean blood pressure for another period of two weeks was 180/100. He was symptomatically improved after a short rest in bed.

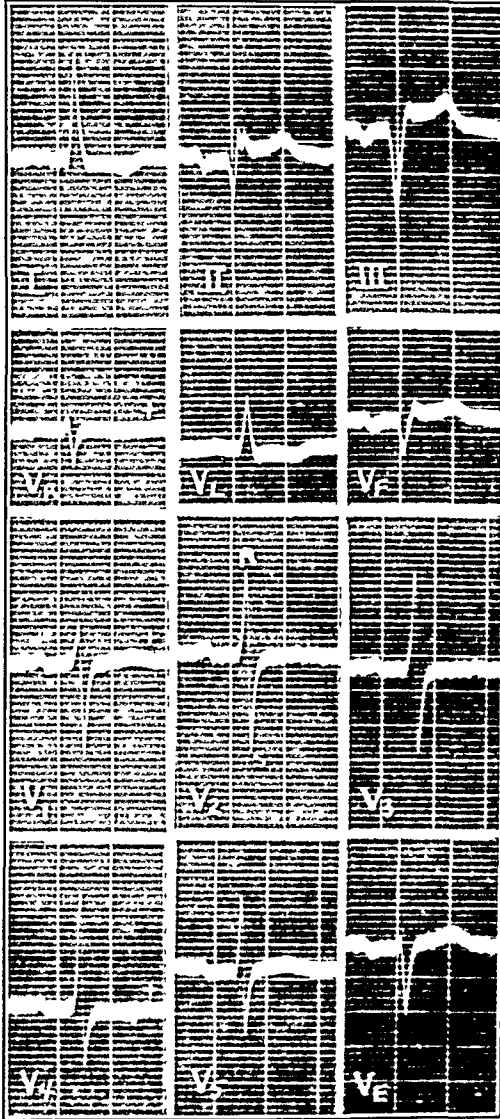


Fig. 1.—Standard and special electrocardiograms in Case 5, patient 65 years of age. The exact time of the coronary occlusion could not be ascertained but was definitely less than one week before the curves were taken. In the special electrocardiograms an upward deflection represents positivity of the exploring electrode. The sensitivity of the string for the standard leads and for the extremity potentials is normal, for the precordial potentials seven-tenths normal (1 mv. = 0.7 cm.). Time lines occur every 0.2 second.

The patient was seen briefly in May, 1934, for progressive blindness in the left eye due to cataract and retinitis. He was not heard from again until congestive heart failure and uremia appeared in March, 1935. The latter was presumably precipitated by an ascending infection of the genitourinary tract, and by retention of urine due to a urethral stricture. Death occurred in coma on April 8, 1935. The nonprotein nitrogen content of the blood was 90 mg. per cent.

The time when myocardial infarction occurred was uncertain, but it was possibly in December, 1933.

Necropsy.—The heart weighed 600 gm. The thickness of the wall of the right ventricle varied from 5 to 8 mm.; of that of the left ventricle from 16 to 22 mm.; and of the interventricular septum from 20 to 25 mm. No evidence of infarction was found until the transverse sections were made. Small areas of fibrosis were

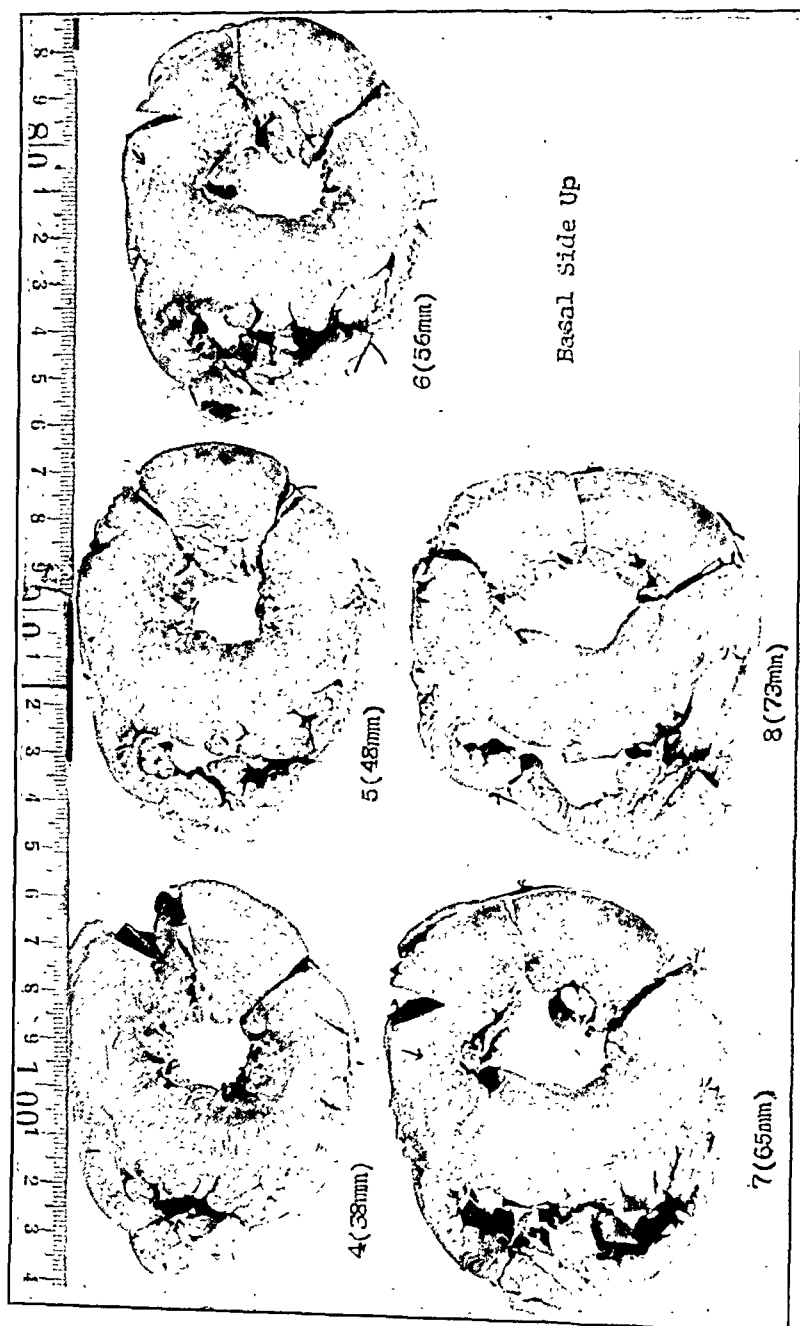


Fig. 2.—Heart sections in Case 6. The basal surfaces are visible, and the anterior wall is below. The infarct is the white area visible in the posterior wall of sections 6 and 7 (arrows). Smaller scars can be seen in the posterior wall of section 4, and in the anterior wall of section 5. The small, dark swelling on the lateral wall of the right ventricle of section 6 is a pericardial cyst.

visible grossly in various parts of the left ventricle. The largest was in the posterior wall at levels of 56 mm. and 65 mm. from the apex, respectively (Fig. 2, sections 6 and 7). It was roughly fusiform in shape, with a length of 15 mm. and a diameter of 5 mm. in its widest part. Its long axis was parallel to the long axis of the heart. Microscopically it consisted of avascular and acellular fibrous tissue.

The morbid anatomy of the coronary arteries was as indicated in Fig. 3. The artery of supply to the scar in the posterior wall of the left ventricle described above was the ramus marginis obtusi. It was occluded by atherosclerosis at its origin from the left ramus circumflexus. Moderate atherosclerosis was present in all of the major coronary branches, as indicated in the figure. The ramus descendens posterior arose anomalously from the left coronary artery.

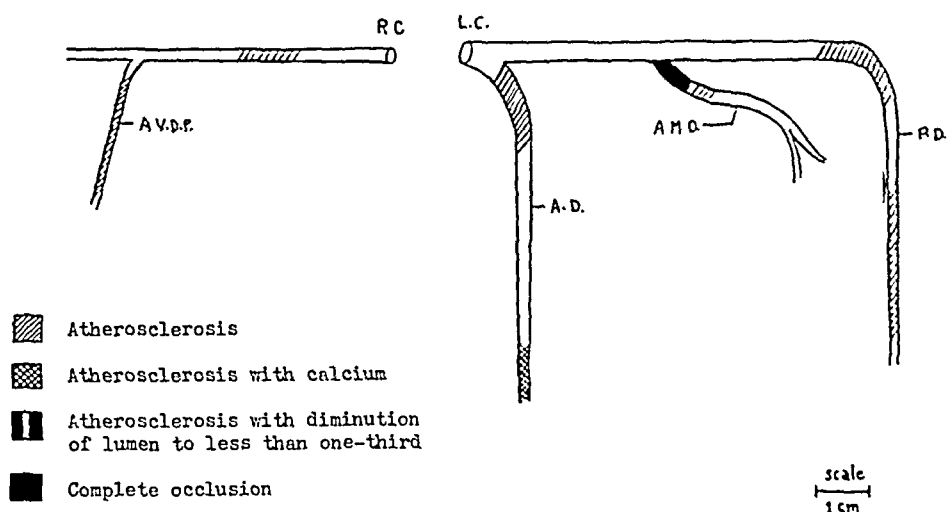


Fig. 3.—Diagram of coronary arteries in Case 6. The ramus descendens posterior arises anomalously from the left coronary artery. L. C., left coronary artery; A. D., ramus descendens anterior; A. M. O., ramus marginis obtusi; P. D., ramus descendens posterior; R. C., right coronary artery; A. V. D. P., ramus ventriculus dexter posterior.

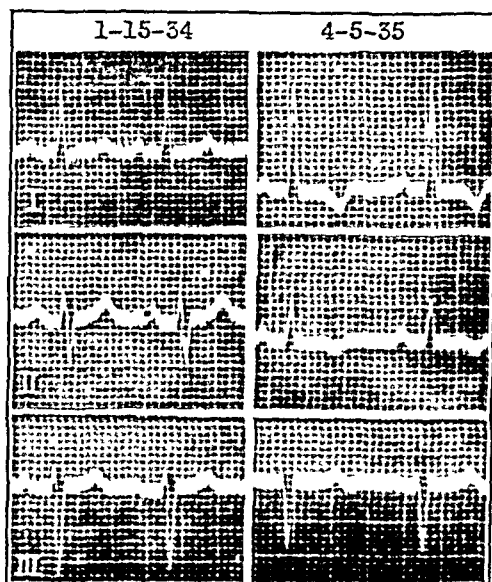


Fig. 4.—Standard electrocardiograms in Case 6, taken approximately fifteen months apart. The string sensitivity is normal. Time lines occur every 0.01 sec.

Electrocardiograms.—Standard electrocardiograms were recorded Jan. 15, 1934, and April 5 and 6, 1935 (Figs. 4 and 5). The first showed a marked sinus arrhythmia and shifting of the pacemaker within the sinus node; the others showed a normal sinus rhythm. The difference between the initial ventricular deflections in the first curve (Fig. 4) and the last two (Figs. 4 and 5) is in part attributable to the fact that the former was taken with the patient seated, the latter while he was

supine. In the second and third electrocardiograms, however, the inverted T wave in Leads I and II could not be ascribed to change in posture alone (Figs. 4 and 5).

Precordial and extremity potentials (Fig. 5) were recorded on April 6, 1935, after the patient had received twelve cat units of digitalis by mouth. This amount had no

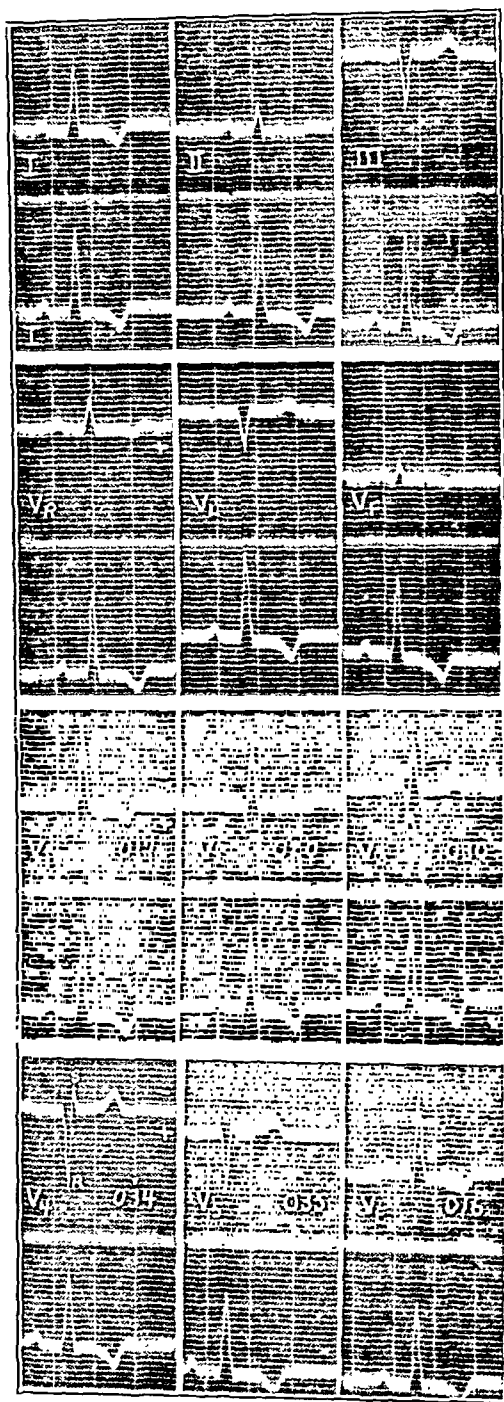


Fig. 5.—Standard leads, extremity potentials, and precordial potentials in Case 6, patient 50 years of age, recorded April 6, 1935, simultaneously with Lead I (lower curve in each illustration). Death occurred two days later. The string sensitivity is half normal for the chest leads, normal for the others. The figure under each precordial lead represents the time in seconds between the peak of R of the chest lead and the beginning of QRS in Lead I. An upward deflection of the string represents negativity of the exploring electrode.

effect on the T wave of the standard leads, and probably little, if any, on the T wave of the special leads. The initial ventricular deflections were not abnormal in the chest leads. The T wave in Leads V_R , V_2 , V_3 , V_4 , and V_5 was abnormal.

DISCUSSION

In accordance with the laws governing electrical currents in volume conductors,⁵⁻⁸ an electrode on the chest will be influenced most by those muscle elements closest to it. The truth of this is borne out by the change in contour of the ventricular complex as an exploring electrode is placed on various parts of the exposed animal^{2, 9, 10} or human¹¹ heart, or on various parts of the animal^{9, 10} or human^{10, 12, 13} precordium. The initial positive deflection, or R wave, of the precordial electrocardiogram is ascribed to the passage of an action current from the endocardium to the epicardium of the muscle near the exploring electrode.¹⁴ It would be expected, therefore, that electrically inactive muscle in the posterior or diaphragmatic regions of the heart would have little effect on the initial ventricular deflections of the precordial electrocardiogram, provided that the muscle of the anterior wall were normal. Cases 5 and 6 are examples. Others have been reported which substantiate these considerations.^{15, 16}

The origin of the deep Q wave in Leads II and III in Case 5 is partly brought to light by a consideration of the extremity potentials (Fig. 1). In a series of thirty normal subjects,¹² the largest Q wave encountered in Lead V_F was 0.12 mv. In Case 5 it was 0.40 mv. Although the infarct was described as being in the posterior wall of the heart, actually, with the heart in the body, it must have been close to, or even resting on, the diaphragm, making its relation to the left leg such that, in effect, this extremity was a semidirect lead from the cavity of the left ventricle.⁹ It was, therefore, negative for the greater part of the QRS interval. Since Lead II is Lead V_F minus Lead V_R , and Lead III is Lead V_F minus Lead V_L , the reason for the deep Q wave in the standard leads becomes clear when the extremity potentials are examined (Fig. 1). This wave is smaller in Lead II than in Lead III because the potential of the right arm is, in the main, negative during the QRS interval, a fact attributed to the circumstance that the right arm is attached to the trunk opposite the auriculoventricular orifices at the base of the heart.¹² If the peak of S in Lead V_R were simultaneous with the peak of Q in Lead V_F , the flow of current through the string would be slight or absent, and it is likely that no Q wave would be found in Lead II. In this instance, however, the peak of S occurred somewhat later and was approximately simultaneous with, and therefore responsible for, the first apex of the R wave in Lead II. Thus, the Q wave in Lead II depends almost entirely upon the negative variation in potential of the left leg. In Lead III, on the other hand, it is almost equally dependent upon the

negative potential of the left leg and the simultaneously positive potential of the left arm.

Abnormalities of the final ventricular deflections (RS-T) of the chest leads in Case 5 are more difficult to explain than the absence of the abnormalities in the initial ventricular deflections. Changes in these waves are sometimes extreme in cases of infarction of the posterior wall;¹⁷ in others they are absent. The reasons for these differences in the electrocardiograms of patients with similar myocardial lesions are at present unexplained.

The cause of the T-wave abnormalities, both in the standard and special leads in Case 6, is not clear. It is probable that ventricular hypertrophy, coronary insufficiency, azotemia, and unknown factors played some part. Considering the nature of the myocardial disease and the inverted T wave in Lead I, it is unlikely that the infarct in the posterior wall was in any way related to the abnormalities noted in the final ventricular deflections. The curves emphasize the fact that T-wave changes may be marked without recent infarction to account for them. These deflections in the chest leads in Case 6 are to be compared with the same leads in Case 4 of Part I.³ The difference between the two is that the T wave in the former is strikingly negative only in those precordial leads (V_4 and V_5) with a large R wave. It will be recalled that the heart in Case 4 showed an infarct in the anterior interventricular septum.

SUMMARY

The potential variations of the extremities and of six precordial points were correlated with the pathologic changes in the hearts in two cases. In the first, a recent infarct extended through the basal portion of the posterior wall of the left ventricle and involved the adjacent interventricular septum. In the second, a small, healed infarct, surrounded by healthy muscle fibers, was present in the basal half of the posterior wall of the left ventricle.

Infarction of the extent found had no appreciable effect on the initial ventricular deflections of the precordial electrocardiograms. In the first case the potential of the left leg (Lead V_F) was, in the main, negative during the inscription of the initial ventricular deflections, presumably because the dead muscle was so oriented that the left leg was a semi-direct lead from the involved area. It is pointed out that this circumstance was the one responsible for the deep Q wave in Lead II, and in part for the deep Q wave in Lead III.

The T-wave abnormalities could be attributed in the case of recent infarction (Case 5) to no anatomic cause other than the infarct itself. In the second case, the T-wave abnormalities were probably not related to the infarcted muscle.

THE PRECORDIAL ELECTROCARDIOGRAM IN MYOCARDIAL INFARCTION

III. OBSERVATIONS ON CASES IN WHICH THE LESIONS WERE DIFFUSE

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ABNORMALITIES that may be observed in the precordial electrocardiogram when there is infarction of the anterior or posterior portions of the heart have been considered previously.^{3, 18} The present article deals with the potential variations of the extremities and of the precordium in three cases in which the cardiac changes were diffuse. The methods were the same as those used in the previous studies.^{3, 18}

REPORT OF CASES

CASE 7.—M. D., a 45-year-old white woman, had polyarthritis at the age of 23 which incapacitated her for six weeks. Thereafter mild joint pains recurred for three or four years. At the age of 43 she was told she had hypertension. It was not until she was 45 that she had cardiac symptoms. The first of these were substernal pain and dyspnea on effort in August, 1934. Progression in the severity of these symptoms made her seek the advice of a physician about the middle of October, 1934. Digitalis and rest in bed caused no improvement.

At 1 A.M. on Oct. 25, the patient had a severe anginal attack accompanied by nausea, vomiting, and collapse. Soon afterward she was admitted to the hospital with pulmonary edema and in shock. The heart sounds were inaudible. The pulse rate was 116 per minute. The blood pressure was 98/70.

The patient partially recovered within the next few hours. During the eighteen days in the hospital, however, attacks of substernal and precordial pain, usually accompanied by dyspnea, cyanosis, nausea, retching, cold sweat, apprehension, rapid pulse rate, and fall in blood pressure occurred almost daily. These would continue for about thirty minutes. When the heart sounds were audible, they were of poor quality. A systolic murmur, a precordial friction rub, and gallop rhythm were noted at one time or another at the cardiac apex.

The mean blood pressure while the patient was in the hospital (seventeen daily readings) was 108/74. The rectal temperature did not exceed 100.6° F. at any time. A blood Wassermann reaction was strongly positive (4 plus).

The patient died during one of the anginal episodes on Nov. 11, 1934, three months after the onset of cardiac symptoms.

Necropsy.—The heart weighed 340 gm. There were several small, opaque, fibrous epicardial patches. The mitral leaflets were vascularized, somewhat thickened by fibrous tissue, and partially fused at the commissures. The myocardium was soft and flabby. In the transverse sections a large scar could be seen extending from epicardium to endocardium in the posterior wall of the left ventricle, near the apex. Toward the base, minute scars were visible in various parts of the left ventricle. In the anterior wall of this chamber, and in the anterior portion of the interventricular septum of the apical sections, the subendocardial myocardium was mottled by

Received for publication May 25, 1939.

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dark red, irregular patches. Three centimeters above the apex this mottling involved the inner half of the entire left ventricular wall and the left side of the anterior one-third of the interventricular septum (Fig. 1). Microscopically, the dark areas consisted of focal hemorrhagic necrosis with early replacement fibrosis which was discernible especially in the posterior wall. The myocardium of the anterior and lateral walls of the right ventricle was extensively infiltrated with fat.

Occlusive disease of the coronary arteries was limited to the ostium and first centimeter of the left main stem. The margins of the ostium were elevated by intimal atheroma. The point of a cartilaginous spicule, 4 mm. in length, protruded from the orifice. The spicule was attached to the walls of the left coronary artery about 3 mm. from the ostium, and almost completely occluded its lumen. In the remainder of its extent the lumen of the artery was greatly reduced in size by intimal thickening. Microscopically, the lesion consisted of irregular intimal and adventitial fibrosis. Some of the vasa vasorum in the aorta adjacent to the mouth of the left coronary showed hypertrophy of the media. There was no evidence of syphilitic mesaortitis. The ramus descendens and the ramus circumflexus of the left coronary artery were free from disease. Slight focal intimal thickening was present in the right coronary artery near its origin.

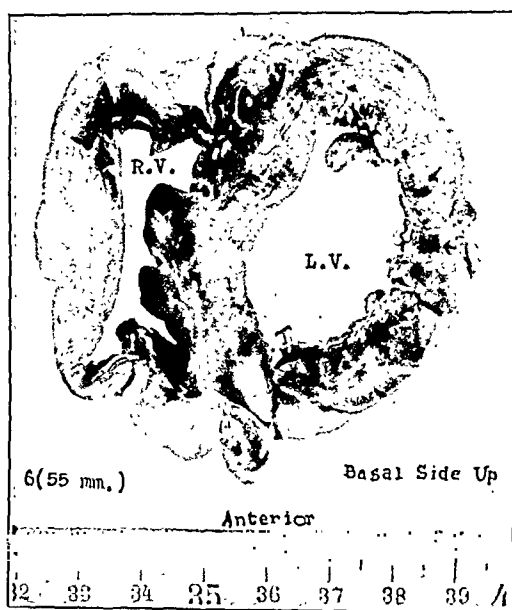


Fig. 1.—Heart section 6, Case 7, basal side up. The dark patches in the subendocardium are areas of hemorrhagic necrosis (arrows). Fine scarring is visible in the septum. The lateral wall of the right ventricle is infiltrated with fat.

Electrocardiograms.—Eight standard electrocardiograms were taken between Oct. 25 and Nov. 7, 1934. All showed sinus rhythm with occasional ventricular premature systoles, and a P-R interval between 0.23 and 0.25 second. The rate of the auricles and of the ventricles ranged between 100 and 120 per minute. In all curves the mean electrical axis was deviated to the left and made an angle with the horizontal (angle alpha) of approximately -38° . The initial and final ventricular deflections were much as they are in the standard leads of Fig. 2, except that in the later curves RS-T displacement was less pronounced. The S wave was prominent in Leads II and III, but no Q wave was present in Lead I.

Potential variations of the extremities and of the precordium were recorded Oct. 25 and 27, 1934. The two sets of curves were almost identical. Those taken

on the latter date are shown in Fig. 2. The potential of the left arm was positive, for the most part, during the inscription of the initial ventricular deflections. The RS-T segment showed slight positive displacement in Lead V_R , and slight negative displacement in Lead V_F . In Leads V_1 , V_2 , V_3 , and V_4 the only initial deflection was a Q wave. The first limb of this deflection was prominently notched in Lead V_2 . The R wave in Lead V_4 and the RS (intrinsicoid) deflection in Lead V_4 and Lead V_5 were abnormally small. The T wave was almost isoelectric in all of the precordial leads.

CASE 8.—G. C., a 52-year-old white man, had an attack of "acute indigestion," characterized by low substernal and epigastric pain, accompanied by dyspnea, in 1928, as a result of which he was in a hospital for five days. Thereafter, he remained well until paroxysms of dyspnea and substernal pain appeared in 1934. These symptoms gradually increased in frequency and severity. At 10 P.M. on Jan. 16, 1935, a severe attack of pain and dyspnea occurred which lasted for five hours. He was admitted to the hospital Jan. 17, soon after its onset. He was dyspneic, orthopneic, and cyanotic. Rales were present in both pulmonary bases, and there was slight pretibial edema. The heart was greatly enlarged. At the apex the first sound was snapping. The ventricular and pulse rates were 96 per minute; the beating was regular. The blood pressure was 165/92 and stayed approximately at this level for the remainder of the patient's life. Two blood Wassermann reactions were moderately (2 plus) and doubtfully (plus-minus) positive, respectively.

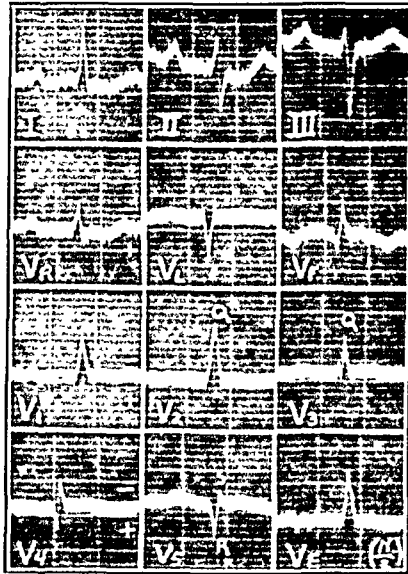


Fig. 2.—Standard and special electrocardiograms in Case 7, patient 45 years of age, recorded Oct. 27, 1934, two weeks before death. An unknown amount of digitalis had been taken by mouth. Standard leads and extremity potentials were recorded with the string at normal sensitivity; precordial potentials were recorded at half-normal sensitivity. An upward deflection represents relative negativity of the exploring electrode. Time lines occur every 0.2 second. The electrocardiograms reproduced in Figs. 6 and 7 were similarly recorded.

The patient improved with rest in bed but continued to have dyspnea which was worse at night. On Jan. 26 he had a slight rise in temperature and complained of a sore throat. The pharynx and tonsils were inflamed. A hemolytic streptococcus grew in the culture of the throat swabbings. Three days later, at 8 P.M., the patient had a severe paroxysm of dyspnea. On Jan. 30 digitalis was started, but no improvement occurred. He died suddenly on Feb. 8, 1935.

Necropsy.—The heart weighed 610 gm. The visceral and parietal pericardium were firmly adherent over the bulging apex and adjacent anterior wall of the left ventricle (Fig. 3). The endocardium of the left ventricular apex, the anterior interventricular septum, and the anterior wall was pale, thick, and opaque. The endocardium of the posterior wall of this chamber and of the nearby septum was dark red in color, and the underlying muscle felt softer than elsewhere. The right ventricle was hypertrophied; its wall measured 1.5 cm. in thickness in its posterior basal portion.



Fig. 3.—Heart in Case 8, viewed from the left. The anterior wall is to the left. The thin, bulging apex, the thick endocardium of apex and septum, and the adherent pericardium (below) are to be noted.

The transverse sections (apical surfaces seen in Fig. 4) showed the diffuse lesions to greater advantage. All that remained of the anterior and lateral portions of the left ventricular apex was a thin layer of muscle, bounded by thick, acellular and avascular endocardium and fibrotic pericardium (Fig. 4, sections 2, 3, and 4). Between the pericardium and the rim of muscle there was a thick layer of fibrolipomatous tissue. This tissue (labeled *A* in sections 3 to 6) was most ex-

tensive in the anterior interventricular sulcus and along the adjacent anterior wall of both ventricles. At the base the layer of myocardium was thicker, and the lesion was limited to the anterior wall of the left ventricle and the nearby thinned septum. Extending from a point about 25 mm. from the apex to the

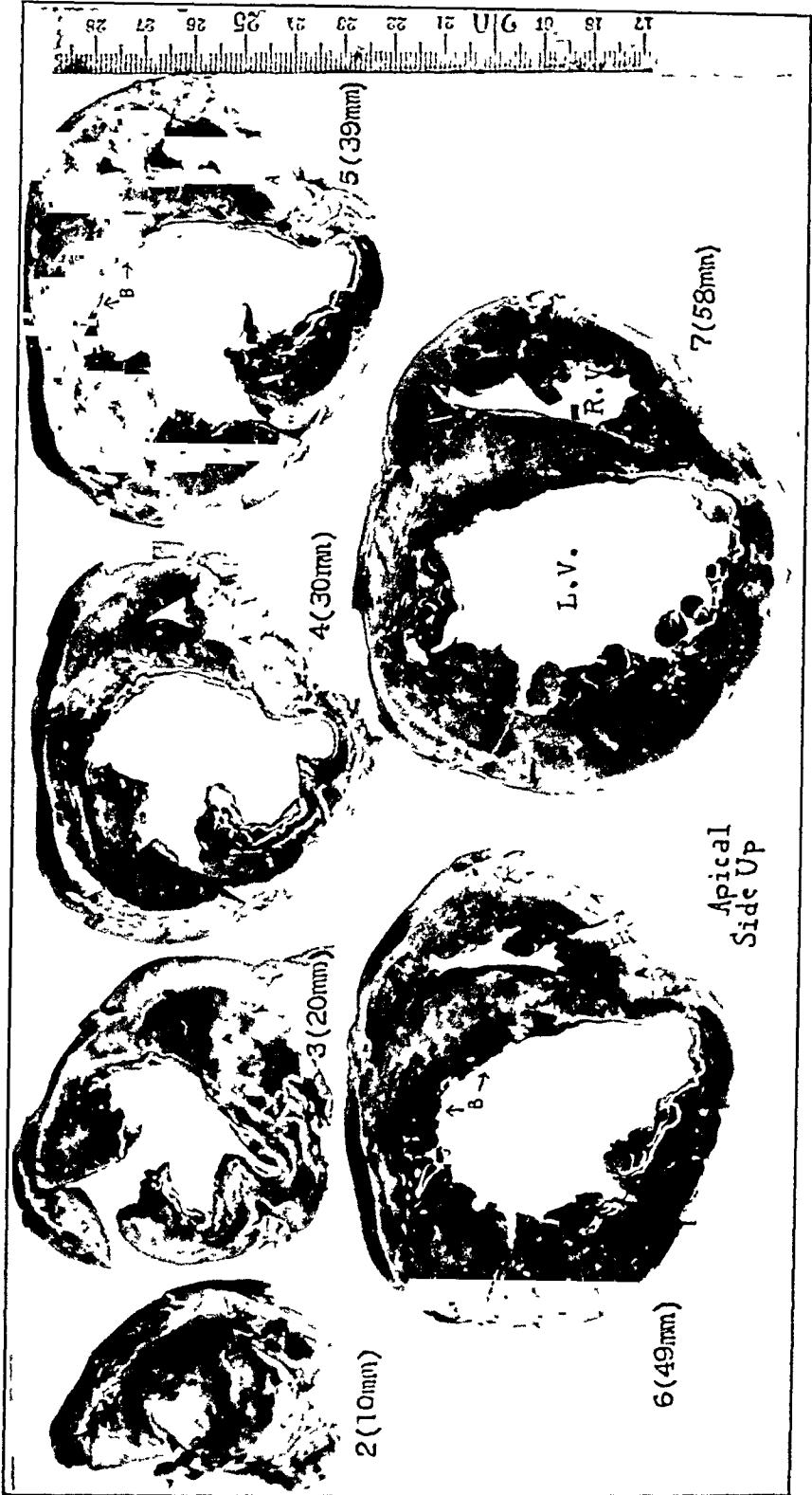


Fig. 1.—Heart sections in Case 8. Contrary to the usual procedure, the apical surfaces of the sections were photographed. The left ventricle is to the left and the anterior wall below. The thick endocardium is white. The increased subepicardial fat is especially prominent in the anterior interventricular groove of sections 4 and 5. The dark areas in the posterior wall B of the basal sections represent hemorrhage into scar tissue. The pericardium is adherent to the apical sections (2 and 3).

basal extremity of the posterior wall, there was a lesion of somewhat different nature (labeled *B* in sections 5 and 6). Grossly, it had a dark red, patchy appearance. It was confined largely to the inner half of the wall and extended somewhat into the left side of the posterior part of the septum. Microscopically, it consisted of scar tissue containing large blood-filled sinusoids and extensive areas of hemorrhage. Near the apex, fresh granulation tissue was seen in the posterior wall, replacing a small area of necrotic muscle cells.

The coronary arteries were extensively diseased (Fig. 5). The first two centimeters of the ramus descendens anterior contained a hyalinized, calcified plaque which decreased the lumen to about one-tenth of its original size. Beyond this obstruction the wall was thick and calcified. The first portions of the ramus circumflexus and of the ramus marginis obtusi were atherosclerotic. The right coronary artery was stenosed at points 0.5 cm. and 5.5 cm. from its origin. Elsewhere there were patchy sclerosis and calcification. Its ramus descendens posterior was calcified in its entire extent, but a sizeable lumen remained.

Electrocardiograms.—Four standard electrocardiograms were taken between Jan. 18 and Feb. 6, 1935. All showed sinus rhythm and a rate between 85 and 110 per minute; a QRS interval of 0.08 to 0.09 second; and a considerable deviation of the electrical axis to the left (angle alpha of approximately -40°). The initial ventricular deflections were similar in all. The Q wave in Lead I and the R wave in Leads II and III were minute deflections, and in some curves an R wave could not be distinguished in Lead II. The S wave in Lead II was slurred, in Lead III, deep. The T wave was inverted in Lead I, isoelectric in Lead II, and upright in Lead III. Only minor differences in this deflection could be discerned in successive electrocardiograms before the administration of digitalis was started.

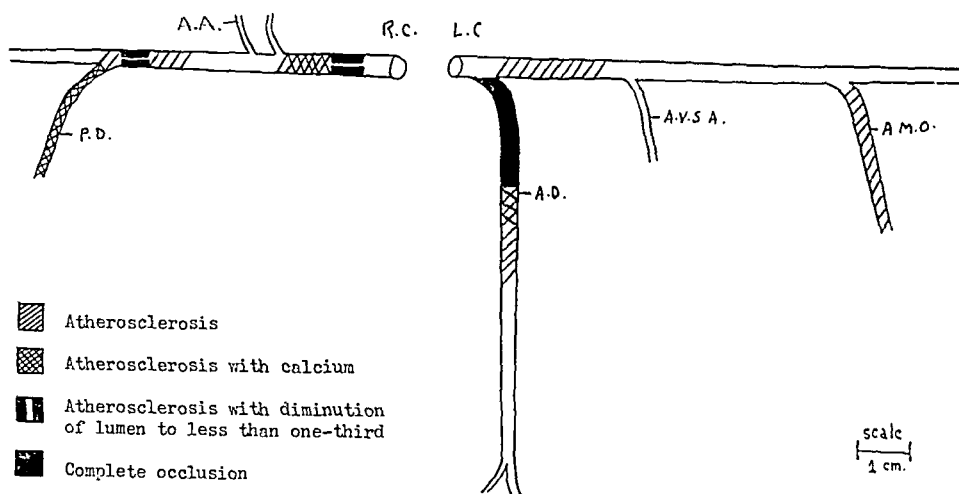


Fig. 5.—Diagram of coronary arteries in Case 8. *L. C.*, left coronary artery; *A. D.*, ramus descendens anterior; *A. V. S. A.*, ramus ventriculus sinister anterior; *A. M. O.*, ramus marginis obtusi; *R. C.*, right coronary artery; *A. A.*, rami auricularis; *P. D.*, ramus descendens posterior.

Extremity and precordial potentials were recorded Jan. 21, 1935 (Fig. 6). Abnormalities in the former were the small T wave in Lead V_R , the large R wave in Lead V_L , and the deep Q wave in Lead V_F . Abnormalities in the initial ventricular deflections of the latter were the small R wave in Leads V_2 and V_3 , the four QRS deflections in Lead V_4 , and the deep S wave in Lead V_6 . Of the final ventricular deflections, the diphasic T wave and the negative T wave in Leads V_4 and V_5 , respectively, were abnormal. Of interest was the QRS interval in Lead V_3 , which measured 0.108 second, compared to that in Lead II, which measured 0.088 second.

CASE 9.—F. C., a 62-year-old white man, was admitted to the hospital May 18, 1936, with congestive heart failure. His mental state was such that a reliable history could not be obtained. He indicated, however, that he had substernal pain.

The heart was enlarged; the sounds were of poor quality. A systolic murmur was heard at the apex, another at the base. The ventricular and pulse rates were 80 per minute. The beating was regular. The blood pressure was 130/50 and averaged 137/63 during the next two weeks. Respiration was of the Cheyne-Stokes type.

Lethargy and dyspnea were prominent symptoms. Digitalis, begun on May 18, was without effect. Splenic enlargement and conjunctival petechiae were noted a few days after admission. A low-grade fever was present. Blood cultures were positive for the *Streptococcus viridans* on three different occasions. Wassermann reactions on the blood and spinal fluid were negative.

Somnolence rapidly deepened to stupor. The patient died May 31, 1936.

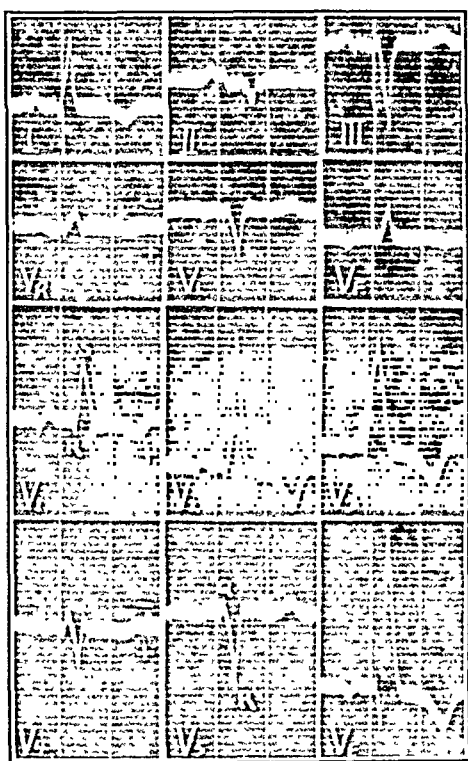


Fig. 6.—Standard leads (I, II, III), extremity potentials (V_r , V_t , V_f), and precordial potentials (V_1 , V_2 , V_3 , V_4 , V_5 , V_6) in Case 8, patient 52 years of age, recorded Jan. 21, 1935, eighteen days before death.

Necropsy.—The heart weighed 500 gm. There was slight sclerosis of the mitral, aortic, and tricuspid valves. Vegetative endocarditis (*Streptococcus viridans*) involved the mitral and aortic leaflets, the chordae tendineae of the anterior mitral leaflet, an area, 2 cm. by 2 cm., of the left auricle just above the posterior mitral leaflet, and a small patch, 0.6 cm. by 1.0 cm., on the left side of the interventricular septum, 0.5 cm. below the aortic valve.

Grossly, the myocardium showed little. The lateral wall of the left ventricle measured 18 to 20 mm. in thickness; that of the right ventricle, 5 to 7 mm. The transverse sections showed slight subendocardial discoloration in the left ventricle, focal endocardial thickening, and focal myocardial fibrosis. On microscopic section, however, there were miliary foci of necrosis, some undergoing replacement fibrosis.

disseminated throughout both ventricles and auricles. These were especially prominent and tended to be confluent in the subendocardial myocardium of the left ventricle. In addition, there were older, loose perivascular and interstitial fibrosis, atrophic muscle cells, and occasional foci of subacute productive myocarditis. The pericardium was focally thickened over both ventricles. The thickened areas were infiltrated by lymphocytes and histiocytes.

The coronary ostia were widely patent. The intima of the ramus descendens anterior was thickened by eccentric hyalinized plaques which, at a distance of 2 cm. from the vessel's origin, reduced its lumen to a diameter of 1 mm. This severe stenosis extended distally for 0.5 cm. The left ramus circumflexus and the right coronary artery showed intimal atheroma in the first few centimeters, but neither of their lumina was appreciably reduced in size.

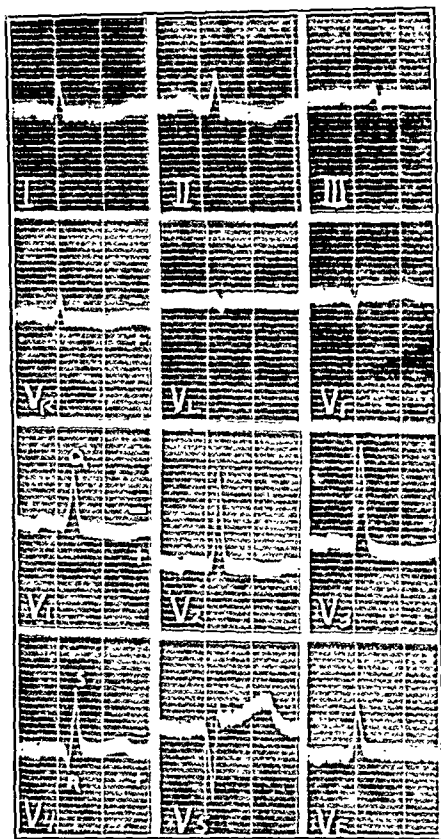


Fig. 7.—Standard and special electrocardiograms in Case 9, patient 62 years of age, recorded eight days before death. A therapeutic dose of digitalis had been administered in the preceding five days.

Electrocardiograms.—Six standard curves were recorded between May 18 and 28, 1936. Only the first of these was obtained before the administration of digitalis was started. The heartbeat had its origin in the sinoauricular node and was regular in all. The rates varied between 90 and 100 per minute. The P-R and QRS intervals were within normal limits. The amplitude of the initial ventricular deflections was low (Fig. 7). In the first electrocardiogram the T wave was low in Lead I, iso-electric in Lead II, and small, but inverted, in Lead III. In all subsequent curves this deflection was inverted in the three leads, though small in Lead III (Fig. 7).

The extremity and precordial potentials (Fig. 7) were recorded May 23, five days after the administration of digitalis was begun, and eight days before the pa-

tient died. A deep Q wave in Leads V_1 and V_F , a small R wave in Leads V_2 , V_3 , and V_4 , and a negative T wave in Leads V_1 and V_2 were the significant abnormalities in the precordial leads. The extremity potentials were small, and the positive T wave in Lead V_R was abnormal. In the special leads little significance could be attached to the abnormal final ventricular deflections because the patient was digitalized.

DISCUSSION

The QRS complexes in the chest leads in Cases 7 (Fig. 2) and 9 (Fig. 7) were rather similar in form. The chief difference between the two was the small R wave in Leads V_2 and V_3 of the latter. In Lead V_3 , in Case 7 (Fig. 2), the R wave was presumably represented by the notch on the first limb of the Q wave.

The resemblance of the disease of the myocardium in these two cases was also striking. In both there was myocardial necrosis which was diffuse but principally located in the subendocardium of the anterior part of the left ventricle. In Case 9 there were, in addition, scattered foci of subacute productive myocarditis. From what was said about the R wave in Part I,³ it seems plausible to assume that the small size or absence of this deflection in several of the leads in the cases under discussion was due to this necrosis.

The changes in QRS of the precordial electrocardiograms were principally in leads from the right side and midportion of the chest. In both of the cases there were lesions in the right ventricle. In one it was extensive fatty infiltration; in the other it was focal myocardial necrosis. It cannot be stated that this disease in the right ventricle had any effect on the chest leads, because, as previously noted,³ the R wave may be absent or diminished in size in leads from the right side of the precordium when disease of the myocardium is limited to the left ventricle and septum. That more marked abnormalities of QRS were not found in leads from the left side of the precordium is probably due to the fact that the lesions were principally in the anterior part of the heart.

Case 8 is unusual in several respects. Considering the extent of the lesion found at necropsy, it is somewhat of a surprise that more marked abnormalities were not present in the extremity and precordial potentials. In Lead V_F the only QRS deflection was a Q wave, 0.35 mv. in size. In the only other case of the series in which this abnormality existed there was a fresh infarct on the posterior wall of the left ventricle (Case 5, reference 8). In Case 8 the lesion on the posterior wall was a scar into which hemorrhage had recently occurred. It would seem that a Q wave in Lead V_F is of some value in localizing electrically inactive muscle in the posterior (diaphragmatic) wall of the heart.

In the chest leads in Case 8 the small R wave was again the most notable feature. The low, though broad, negative deflection in Lead

V₄, which ordinarily would be designated as Q, was in this instance preceded by a minute positive deflection, an explanation for which is lacking.

The QRS interval of 0.106 sec. in Lead V₃, compared to an interval of 0.088 in Lead III, is of interest. Such a discrepancy must occur more frequently than is suspected, for the standard leads represent the difference in potential between two extremities, and if the potential of these extremities varies in a similar manner either at the beginning or end of the initial ventricular deflections, no current will flow through the string, and the QRS interval will be correspondingly shortened. Further, the standard leads record electrical forces in the frontal plane, or those making a relatively acute angle with this plane. Currents generated in the anteroposterior plane affect all three extremities similarly. Therefore, they cause no deflection in the standard leads but may cause a sizeable one in the chest leads. This would, conceivably, account for variations in the QRS interval in the two types of leads. Differences in the duration of QRS in different chest leads are due, at least in part, to this same factor.

The factors responsible for abnormalities of the T wave in the cases just discussed are so numerous that more than mention of them does not seem justified at this time.

SUMMARY

The potential variations of the extremities and of six precordial points were correlated with the diffuse lesions found in the hearts in three cases. In two of these the changes were similar. In one they consisted of disseminated miliary necrosis and foci of subacute productive myocarditis in both ventricles; in the other there were acute, healing, and healed focal necrosis of the left ventricle and septum, and fatty infiltration of the right ventricle. The QRS complexes of the special electrocardiograms were similar to each other in these two cases and simulated those seen with various degrees of infarction of the anterior wall of the left ventricle. In the remaining case the infarct consisted of old fibrous tissue, located anteriorly and posteriorly. The posterior portion was electrocardiographically reflected in the extremity leads by a deep Q wave in Lead V_F. The anterior portion was held responsible for the low R wave in leads from the right side and midportion of the precordium, and for a prominent early negative deflection in Lead V₄.

REFERENCES

PARTS II AND III

1. Wilson, F. N., Macleod, A. G., and Barker, P. S.: *Electrocardiographic Leads Which Record Potential Variations Produced by the Heart Beat at a Single Point*, Proc. Soc. Exper. Biol. and Med. 29: 1011, 1932.
2. Wilson, F. N., Johnston, F. D., Macleod, A. G., and Barker, P. S.: *Electrocardiograms That Represent the Potential Variations of a Single Electrode*, AM. HEART J. 9: 447, 1934.

3. Kossmann, C. E., and de la Chapelle, C. E.: The Precordial Electrocardiogram in Myocardial Infarction. I. Observations on Cases With Infarction Principally of the Anterior Wall of the Left Ventricle and Adjacent Septum, *AM. HEART J.* 15: 700, 1938.
4. Macleod, A. G., Wilson, F. N., and Barker, P. S.: The Form of the Electrocardiogram. I. Intrinsicoid Electrocardiographic Deflections in Animals and Man, *Proc. Soc. Exper. Biol. and Med.* 27: 586, 1930.
5. Wilson, F. N., Wishart, S. W., Herrmann, G. R.: Factors Influencing Distribution of Potential Differences Produced by Heart Beat at Surface of Body, *Proc. Soc. Exper. Biol. and Med.* 23: 276, 1926.
6. Canfield, R.: On the Electrical Field Surrounding Doublets, and Its Significance from the Standpoint of Einthoven Equations, *Heart* 14: 102, 1927.
7. Craib, W. H.: A Study of the Electrical Field Surrounding Active Heart Muscle, *Heart* 14: 71, 1927.
8. Wilson, F. N., Macleod, A. G., and Barker, P. S.: The Distribution of the Currents of Action and of Injury Displayed by Heart Muscle and Other Excitable Tissues, *University of Michigan Studies, Scientific Series, Vol. X. U. of Mich.*, 1935.
9. Wilson, F. N., Hill, I. G. W., and Johnston, F. D.: The Form of the Electrocardiogram in Experimental Myocardial Infarction.
 - I. Septal Infarcts and the Origin of the Preliminary Deflections of the Canine Levocardiogram, *AM. HEART J.* 9: 596, 1934.
 - II. The Early Effects Produced by Ligation of the Anterior Descending Branch of the Left Coronary Artery, *AM. HEART J.* 10: 889, 1935.
 - III. The Later Effects Produced by Ligation of the Left Coronary Artery, *AM. HEART J.* 10: 903, 1935.
 - IV. Additional Observations on the Later Effects Produced by Ligation of the Anterior Descending Branch of the Left Coronary Artery, *AM. HEART J.* 10: 1025, 1935.
 - V. The Later Effects Produced by Ligation of the Right Coronary Artery, *AM. HEART J.* 16: 309, 1938.
10. Wilson, F. N., Macleod, A. G., and Barker, P. S.: The Onset of Ventricular Excitation in Human Bundle-Branch Block, *AM. HEART J.* 7: 305, 1932.
11. Barker, P. S., Macleod, A. G., and Alexander, J.: The Excitatory Process Observed in the Exposed Human Heart, *AM. HEART J.* 5: 720, 1930.
12. Kossmann, C. E., and Johnston, F. D.: The Precordial Electrocardiogram. I. The Potential Variations of the Precordium and of the Extremities in Normal Subjects, *AM. HEART J.* 7: 925, 1935.
13. Wilson, F. N., Macleod, A. G., Barker, P. S., Johnston, F. D., and Klostermeyer, L. L.: The Electrocardiogram in Myocardial Infarction With Particular Reference to the Initial Deflections of the Ventricular Complex, *Heart* 16: 155, 1933.
14. Wilson, F. N., Johnston, F. D., and Hill, I. G. W.: The Interpretation of the Galvanometric Curves Obtained When One Electrode Is Distant From the Heart and the Other Near, or in Contact With the Ventricular Surface. Part II. Observations on the Mammalian Heart, *AM. HEART J.* 10: 176, 1934.
15. Wood, F. C., Bellet, E., McMillan, T. M., and Wolferth, C. C.: Electrocardiographic Study of Coronary Occlusion, *Arch. Int. Med.* 53: 752, 1933.
16. Wilson, F. N.: The Electrocardiogram in Diseases of the Coronary Arteries. Ch. XII in *Diseases of the Coronary Arteries and Cardiac Pain*, by R. L. Levy, New York, 1936, The Macmillan Company.
17. Wood, F. C., and Wolferth, C. C.: Huge T-waves in Precordial Leads in Cardiac Infarction, *AM. HEART J.* 9: 706, 1934.
18. Kossmann, C. E., and de la Chapelle, C. E.: The Precordial Electrocardiogram in Myocardial Infarction. II. Observations on Cases With Infarction of the Posterior Wall of the Left Ventricle, *AM. HEART J.* 18: 344, 1939.

METHOD FOR THE STUDY OF VENTRICULAR FIBRILLATION

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INVESTIGATORS have hitherto relied mainly on electric shock to produce experimental ventricular fibrillation.^{1, 2, 3, 4} For quantitative studies the intensity of electrical stimulation necessary to produce ventricular fibrillation under varying conditions has been determined, and electrocardiograms have been obtained either by limb leads, or directly from the exposed heart. Extensive studies^{2, 4} have been made of the effect of drugs on electrically produced fibrillation.

With these methods, however, many complicating factors are involved, since the heart may also be affected indirectly by changes produced in other parts of the body. The aim of the present study was to confine the action to the heart alone, so as to be able to determine a 'fibrillation level' for the myocardium under standard, controlled conditions. For this purpose the isolated, perfused heart was used, and ventricular fibrillation was produced by the action of barium chloride.

METHOD

The heart of the cat, dog, or rabbit was isolated immediately after death by bleeding and was perfused through the coronary system with oxygenated Locke's solution by a modification of the Langendorff method. The temperature of the heart and perfusing fluid was kept constant at 38° C. by means of a water bath and warm chamber controlled by a thermostat, and the perfusion pressure was maintained at 80 mm. Hg for the rabbit heart, and 100 mm. Hg for the cat or dog heart. Slight changes of the perfusion pressure did not appear to affect the results. Perfusion was continued usually for ten or fifteen minutes, until the heart was beating steadily, and the coronary flow, measured approximately by collecting the outgoing fluid, was constant. Then, without alteration of pressure or temperature, the perfusate was changed to Locke's solution containing 0.2 per cent barium chloride, and the outgoing fluid was collected from the commencement of barium perfusion until the moment of onset of ventricular fibrillation. From the volume of this fluid the total amount of barium chloride which passed through the coronary system during that period was calculated. Allowance was made for the small amount of perfusate containing no barium, namely, that which occupied the short length of tube between the point of entry of the solution and the heart.

At the end of the experiment the heart was removed from the apparatus and weighed, and the number of milligrams of barium chloride per gram of heart tissue necessary to produce fibrillation was calculated.

In the earlier experiments the ventricular contractions were recorded graphically, but later it was found that the exact instant of onset of fibrillation could be determined more accurately by direct inspection.

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Received for publication April 22, 1939.

RESULTS

Table I shows the results of such experiments. It will be seen that the average amount of barium chloride per gram of heart tissue necessary to produce fibrillation was 1.87 mg. for the rabbit heart, 1.38 mg. for the cat heart, and 0.83 mg. for the dog heart. The rabbit heart, therefore, required the largest amount, the dog heart the least, and the cat heart was intermediate. This is in keeping with the observation of Garrey,⁵ and others, that large hearts fibrillate more readily than small ones. Indeed, Garrey states that the tendency to recover from fibrillation is in inverse ratio to the tissue mass.

The cat heart is undoubtedly the most suitable for this type of experiment. The rabbit ventricles in some cases will not fibrillate at all, and the transition from coordinated beating to fibrillation is occasionally so gradual that it is difficult to identify the instant of onset. The dog heart, on the other hand, perhaps owing to the unsuitability of Locke's solution as a perfusate for large hearts, exhibits a tendency to spontaneous fibrillation and to various degrees of heart block which makes it unreliable as a standard.

The average amount of barium chloride per gram of cat heart necessary to produce fibrillation under these standardized conditions appears to be 1.38 mg. In order to ascertain whether this "fibrillation level" can be altered by drugs known to affect fibrillation induced by other means, we also investigated the effects of quinidine and digitalis on the onset of "barium" fibrillation. Quinidine has been found both experimentally⁴ and clinically⁶ to render the heart refractory to stimuli that would ordinarily throw it into ventricular fibrillation. To determine whether it would have a similar effect upon the fibrillation induced by barium, further experiments were performed, in which 0.75 mg. of quinidine was added to each liter of the Locke's solution perfused through the cat heart. After perfusion with as little as 20 to 50 c.c. of this solution, the heart beat more slowly and the strength of ventricular contraction increased. At this point, usually about five minutes after the onset of quinidine perfusion, barium chloride was introduced as described above, and the amount necessary to cause ventricular fibrillation was ascertained. The results are shown in Table II.

These experiments indicate that quinidine has a definite protective action against the ventricular fibrillation induced by barium, since the average amount of barium chloride required was raised from 1.38 to 2.52 mg. per gram of heart tissue. Moreover, the type of fibrillary movement was altered by quinidine. Ordinarily, after perfusion with barium, the cat's ventricular musculature exhibited fine, rapid, vermiform movements, but when the barium was preceded by quinidine, the fibrillary movements consisted of large, slow-moving, coarse undulations, sweeping over the ventricles.

TABLE I
AMOUNT OF BaCl₂ NECESSARY TO PRODUCE VENTRICULAR FIBRILLATION IN ISOLATED PERFUSED HEARTS

RABBIT					CAT				DOG					
NO.	C.C. BaCl ₂	% BaCl ₂	WT. OF HEART IN GM.	MG. BaCl ₂ PER GM. HEART	NO.	C.C. BaCl ₂	% BaCl ₂	WT. OF HEART IN GM.	MG. BaCl ₂ PER GM. HEART	NO.	C.C. BaCl ₂	% BaCl ₂	WT. OF HEART IN GM.	MG. BaCl ₂ PER GM. HEART
1	5	0.2	5.5	1.8	1	14	0.3	21.5	1.96	5	37	0.3	83.5	1.3
2	6	0.2	6.5	1.8	2	8	0.3	17.5	1.37	6	24	0.3	99.5	0.72
3	5	0.2	6.0	1.7	3	7	0.3	15.0	1.40	7	29	0.3	90.5	0.90
4	6	0.2	6.5	1.8	4	13	0.3	14.5	2.68	17	50	0.3	115.0	1.3
5	did not fibrillate				5	10	0.2	17.0	1.18	18	30	0.3	80.0	1.14
6	did not fibrillate				6	15	0.2	25.0	1.20	19	30	0.15	97.0	0.48
7	4	0.2	5.4	1.8	7	8	0.2	12.5	1.28	20	60	0.10	79.0	0.76
8	did not fibrillate				8	12	0.2	26.5	0.91	21	24	0.2	65.5	0.74
9	7	0.2	5.4	1.8	9	7	0.2	14.5	0.97	22	18	0.2	65.5	0.54
10	6	0.2	4.9	2.4	10	10	0.2	12.0	1.67	23	59	0.2	108.0	1.1
11	3	0.2	4.2	1.4	11	7	0.2	13.0	1.08	24	32	0.2	111.0	0.58
12	5	0.2	4.5	2.2	12	10	0.2	16.0	1.25	25	66	0.15	86.0	1.1
13	5	0.2	5.3	1.8	13	8	0.2	16.0	1.00	26	40	0.15	94.0	0.63
14	6	0.2	6.2	1.9	20	9	0.2	13.0	1.38	27	84	0.15	163.0	0.56
15	5	0.2	5.5	1.9						28	36	0.15	81.5	0.66
Average				1.87	Average				1.38	Average				0.83

TABLE II

AMOUNT OF BaCl_2 REQUIRED TO PRODUCE VENTRICULAR FIBRILLATION IN QUINIDINIZED HEARTS

NO.	C.C. BaCl_2	% BaCl_2	WT. OF HEART IN GM.	MG. BaCl_2 PER GM. HEART	COMMENT
Q1	13	0.2	8.6	3.0	Coarse fibrillation
Q2	17	0.2	14.1	2.4	Coarse fibrillation
Q3	22	0.2	18.2	2.4	Coarse fibrillation
Q4	10	0.2	16.5	1.2	Extremely coarse fibrillation
Q5	13	0.2	7.6	3.4	Extremely coarse fibrillation
Q6	34	0.2	15.6	4.4	Extremely coarse fibrillation
Q7	10	0.2	15.5	1.3	Extremely coarse fibrillation
Q8	14	0.2	16.0	1.8	
Q9	16	0.2	16.2	2.0	
Q10	16	0.2	9.7	3.3	
Average				2.52	

The fact that quinidine increases the amount of barium chloride necessary to produce fibrillation leads us to believe that this method can be used to demonstrate elevation of the threshold for the initiation of fibrillary movements.

In order to find out whether the method could also detect a lowering of the fibrillation threshold, we performed similar experiments, using digitalis instead of quinidine. The cat heart was first perfused with Locke's solution containing 0.5 cat unit of digitalis per liter. As before, perfusion was continued until some irregularity in rhythm developed, or the contractile power of the heart was visibly altered, and then perfusion with barium chloride was started and the amount necessary to produce ventricular fibrillation determined.

Table III shows that after digitalis the average amount of barium chloride was decreased from 1.38 to 0.81 mg. per gram of heart tissue. It seems, therefore, that a lowered threshold for fibrillation can also be detected by this method.

TABLE III

AMOUNT OF BaCl_2 REQUIRED TO PRODUCE VENTRICULAR FIBRILLATION IN DIGITALIZED HEARTS

NO.	C.C. BaCl_2	% MG. BaCl_2	WT. OF HEART IN GM.	MG. BaCl_2 PER GM. HEART
D1	10	0.2	23.1	0.86
D2	11	0.2	26.9	0.82
D3	9	0.2	19.0	0.94
D4	5	0.2	14.0	0.72
D5	5	0.2	13.8	0.72
Average				0.81

SUMMARY

By means of perfusion with barium chloride, the "fibrillation level," or tendency of the heart to fibrillate, may be measured, and the effects of drugs on this level may be studied.

REFERENCES

1. Braun, L., and Samet, B.: Studien über Herzkammerflimmern, *Arch. f. exp. Path. und Pharm.* 159: 54, 1931.
2. Van Dongen, K.: The Action of Some Drugs on Fibrillation of the Heart, *Arch. Int. de Pharmacodyn. et de Therapie* 53: 80, 1936, and 54: 252, 1936.
3. Williams, H. B., King, B. G., Ferris, L. P., and Spence, P. W.: Susceptibility of Heart to Electric Shock in Different Phases of the Cardiac Cycle, *Proc. Soc. Exp. Biol. and Med.* 31: 873, 1934.
4. Levine, H. D.: Effect of Quinidine Sulphate in Inhibiting Ventricular Fibrillation, *Arch. Int. Med.* 49: 808, 1932.
5. Garrey, W. E.: Auricular Fibrillation, *Physiol. Rev.* 4: 215, 1924.
6. Dock, W.: Transitory Ventricular Fibrillation as a Cause of Syncope and Its Prevention by Quinidine Sulphate, *AM. HEART J.* 4: 709, 1929.

Department of Clinical Reports

PERICARDITIS WITH EFFUSION DUE TO THE MENINGOCOCCUS

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MENINGOCOCCIC infections present themselves, as a rule, in the form of acute, subacute, or chronic infections of the blood stream, with or without later metastatic localization in the meninges. The localization of meningococcal infection within the pericardium is distinctly rare, and a single case, presenting itself as a primary problem in pericardial effusion, is sufficiently unique to warrant a brief report.

Bettencourt and Franga,¹ in 1904, mentioned three cases of pericarditis complicating meningococcus meningitis, in two of which organisms were recovered by smear and culture. Weichselbaum and Ghon,² in 1905, reported an instance of meningococcal endocarditis and pericarditis, but the organisms were not recovered from the pericardium. In the same year, Lenhartz³ recorded one case of proved purulent meningococcal pericarditis, and Elser,⁴ in a review of 23 autopsies on patients with meningococcal meningitis, found five cases of pericarditis, the sacs containing 5 to 35 c.c. of seropurulent or purulent fluid. In two instances, organisms were seen in the smear and, in one instance, were recovered by culture. Duval,⁵ in 1908, reported the case of a child, 7 years old, with meningitis and fibrinopurulent pericarditis, in which the organisms were obtained from the pericardial fluid by smear and culture. It is important to note that in all of the above cases of pericarditis there was an associated meningitis, and that all of the patients died.

Herrick,⁶ in 1918, reviewed the essential features of 12 cases of meningococcal pericarditis which occurred during an epidemic of 280 cases of meningitis and pointed out that pericarditis is usually a complication of serious meningococcal sepsis. Six patients presented effusions varying in amounts from 30 c.c. to 640 c.c.; the remaining six were of the "dry" type. In four cases, the diagnosis was made during life, and two of the patients recovered. Of those who recovered, one had the largest effusion, 640 c.c. of purulent fluid, in which organisms were demonstrated by smear and culture; the other presented only an audible pericardial friction rub. Zuccola,⁷ in 1929, reported an instance of a young man with meningococcemia and meningitis from whose pericardial sac a few cubic centimeters of purulent fluid were removed, but no organisms were identified. Recovery followed serum therapy. Trace and Berkovitz.⁸

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Received for publication Feb. 6, 1932.

in 1931, recorded the case of a boy, aged 13 years, with meningococcic meningitis, who developed a pericardial friction rub on the fifth day of his disease. Pericardial paracenteses on two occasions yielded small amounts of seropurulent fluid containing a few intracellular, Gram-negative diplococci, but no organisms were grown on culture. Recovery followed intraspinal, subcutaneous, intramuscular, and intrapericardial injection of serum. In his review of the subject of meningococcic myocarditis, Saphir,⁹ in 1936, mentioned one case in which the pericardial sac contained 150 c.c. of seropurulent fluid, but bacteriologic examination of the fluid was not reported. The occurrence of pericarditis in meningococcic infections is mentioned by several authors,^{10, 11, 12} but little comment is made except by Adshead,¹⁰ who ascribed the pericarditis to serum therapy in four cases, in all of which the patients recovered. It is interesting that several reviews of pericarditis,^{13, 14, 15} meningococcemia,¹⁶ and the newer reference texts^{17, 18} fail to mention the meningococcus as an etiologic agent in pericarditis.

CASE REPORT

History.—R. W., a white, 32-year-old minister, entered the hospital March 30, 1938, with the primary complaint of dull, constant, aching substernal pain, of two weeks' duration. The family, marital, and past histories were noncontributory. In general, his health always had been good. The history of his present illness revealed that he was in good health until 16 days prior to entry, when he had two impacted wisdom teeth removed. He felt perfectly well until the second post-operative day, when he noted that the left side of his neck ached and was mildly stiff; this remained so for about two days. Four days after the operation he developed dull, constant, aching substernal pain. Six hours after the onset of chest pain, he was seen by his physician, who discovered that his temperature was 102° F., by mouth. Sulfanilamide and analgesics were administered. He remained in bed for about two days, his fever subsided, and the pain disappeared. He then arose and resumed his normal duties, but he felt somewhat weak; however, he was able to play eighteen holes of golf on three of the next six days with but slight dyspnea. Three days prior to his entry there was a return of the dull aching substernal pain, and a roentgenogram of the chest showed cardiac enlargement. He resumed complete bed rest until admission to the hospital, to which he came because of pain, low-grade fever, and moderate dyspnea.

Physical Examination.—The temperature was 38.4° C., the pulse rate, 84; the respiratory rate, 26; and the blood pressure 110/70. The patient was a slender, fairly well-developed, intelligent, cooperative young white man, appearing ill, with moderate dyspnea and orthopnea. No petechiae or skin eruptions were seen. There was no generalized lymphadenopathy. The eyes and ears showed no abnormalities. The nasal septum was deflected to the left, with considerable obstruction to breathing space. The existing teeth were in good condition; no pyorrhea was present. The neck veins showed moderate engorgement; the trachea was in the midline; the thyroid gland was not enlarged. The lungs showed dullness and diminished breath sounds at the right base, with moist crepitant râles bilaterally. The heart was markedly enlarged to the right and left, with obliteration of the pericardial angle on the right. The apex impulse was not seen or felt. The heart sounds were distant and much diminished in intensity; no murmurs were heard. The rhythm was normal. The peripheral vessels showed no thickening. The pulse was of small volume, with a distinct paradoxical character both to palpation and

manometric readings. A tender liver was palpated about five centimeters below the right costal margin. The spleen was not felt, and no ascites was demonstrated. Genital and rectal examinations showed nothing remarkable. The extremities were grossly normal. No edema was noted.

Laboratory Data.—The hemoglobin was 13 grams; the erythrocyte count, 3,782,000; the color index, 1.1; and the leucocyte count 9,400. The differential leucocyte count showed polymorphonuclear leucocytes, 84 per cent; basophils, 2 per cent; monocytes, 2 per cent; large lymphocytes, 3 per cent; and small lymphocytes, 9 per cent. The sedimentation rate was 26 mm. per hour, corrected. Repeated urinalyses and stool examinations were negative. Roentgenologic examination of the chest showed generalized pulmonary congestion, with fluid at the base of the right lung and enlargement of the cardiac silhouette both to the right and left. The electrocardiogram showed normal sinus rhythm, a rate of 104, no abnormal axis deviation, normal P-R and QRS intervals, borderline voltage, with a maximum deflection of plus 6 in Lead II, an isoelectric to inverted T₁, an upright T₂ and T₃; and a normal precordial lead. The borderline voltage, plus the T-wave inversion, was entirely consistent with pericardial disease. The blood culture was negative. Tuberculin tests were negative.

Course in the Hospital.—During the first few hospital days his temperature persisted at a level of about 38° C. On the fourth day pericardial paracentesis was performed; 200 c.c. of thin, serosanguineous fluid were removed, and replaced by 150 c.c. of air. The fluid clotted quickly; its specific gravity was 1.030. A cell count revealed 2,550 leucocytes per cmm., of which 8 per cent were polymorphonuclear neutrophils, and 92 per cent, lymphocytes. Smears revealed Gram-negative diplococci. The organisms were grown in culture and identified as meningococci (*N. intracellularis*). The agglutination titer, using the patient's serum and organisms, was 1-40. Dramatic improvement followed the paracentesis. His temperature remained normal for six days, the pulmonary congestion quickly receded, and the venous pressure diminished. A teleoroentgenogram showed a thickened pericardium enclosing fluid and air. On the tenth hospital day an unsuccessful pericardial paracentesis was performed. Two days later his temperature rose to 39° C., consolidation appeared in the lower lobe of the right lung, and two successive blood cultures were positive for *N. intracellularis*. Sulfanilamide administration was begun immediately, in doses of 4.8 gm. per day for a period of eighteen days, with improvement manifested by the gradual return of his temperature to normal and the disappearance of all signs of pericardial effusion and lung consolidation. A thrombophlebitis of the right leg, which developed during this period, also cleared up. Blood cultures became negative and remained so throughout his hospital course. Cultures from the nose, mouth, and throat were negative for *N. intracellularis*. On the fortieth hospital day, after five days of normal temperature, a fever of 38° C. to 39° C. reappeared. Antimeningococcic serum was administered in a quantity of 165 c.c. over a six-day period; it was given intramuscularly because of violent reactions to intravenous injection. Serum sickness developed, but no other significant response to serum therapy was noted. Sulfanilamide was given again on the forty-seventh hospital day and continued for one week. His temperature fell to normal, and remained so until his discharge on the fifty-sixth hospital day. By this time all symptoms and signs had disappeared, and fluoroscopic examination of the heart and lungs showed nothing abnormal. Immune antibodies developed in the patient's blood, as evidenced by agglutinins in a serum dilution of 1-1280, bacteriolysins in a serum dilution of 1-100, and marked opsonophagocytosis. The patient has been followed for 7 months since his discharge by his own physician, who reports his health to be excellent and his heart normal to physical examination.

DISCUSSION

This case represents a rare instance of meningococcic infection producing typical pericardial effusion with cardiac tamponade. There was no history to suggest meningococcemia or meningitis as a preliminary to the development of pericarditis. This is particularly interesting, for in the previously reported cases there has been, almost invariably, an accompanying meningitis. The usual portal of entry in meningococcic infections is believed to be the upper respiratory passages, and it is possible that the organisms were introduced into the blood stream at the time he had his teeth extracted,¹⁹ with subsequent metastatic localization in the pericardium. This was probably the only focus of infection at the time of admission. Cultures from the nose, mouth, and throat were all negative for meningococci. It is noteworthy that pericardial paracentesis yielded thin, serosanguineous fluid containing a small number of cells, largely lymphocytes, and organisms which were demonstrated by smear and culture. The blood culture, while initially negative, became positive for several days following a second and unsuccessful paracentesis. It is conceivable that the organisms gained entrance to the blood stream at this time. Following the removal of the effusion, with subsequent relief of cardiac tamponade, the problem in therapy shifted from one primarily cardiac to that of meningococcemia. Sulfanilamide alone was ineffective in controlling the disease, but when it was given in conjunction with antimeningococcic serum recovery was complete. The development of immune antibodies in high titer in the blood stream is supportive evidence of cure.

Meningococcic pericarditis produces no symptoms or signs distinctive of the causative organism. While it is usually a feature of the late period of the acute stage of the disease,⁶ and is generally seen with meningitis, it need not necessarily be associated with meningococcemia, meningitis, or other severe complications. The pericarditis may be evidenced by signs varying from a simple friction rub to those of a large effusion, which may be serous, purulent, sanguineous, or combinations of these, and may contain predominantly lymphocytes or polymorphonuclear leucocytes.

Treatment consists of paracentesis, if effusion is present, sulfanilamide, and antimeningococcic serum, which should be administered intrapericardially as well as intravenously, as first suggested by Herrick. The mortality in the reported cases is definitely high, but this is more likely attributable to the preceding serious infection than to the pericarditic complication. It is suggested that in those cases of pericardial effusion in which organisms are not easily demonstrated, care should be taken to rule out meningococcic infection.

CONCLUSION

1. An instance of meningococcic infection producing pericardial effusion with cardiac tamponade is reported.

2. Complete recovery followed pericardial paracentesis and treatment with sulfanilamide and antimeningococcic serum.

REFERENCES

1. Bettencourt, A. and Franca, C.: Über die Meningitis cerebrospinalis epidemica und ihren spezifischen Erreger. *Zeits. f. Hyg. und Inf.* 46: 463, 1904.
2. Weichselbaum, A. and Ghon, A.: Der *Micrococcus meningitidis cerebrospinalis* als Erreger von Endokarditis sowie sein Vorkommen in der Nasenhöhle Gesunder u. Kranker. *Wien. Klin. Wchnschr.* 18: 625, 1905.
3. Lohr, Hermann: Über die epidemische Genickstarre. *Deutsch. Arch. f. Klin. Med.* 84: 51, 1905.
4. Elser, William J.: A Contribution to the Study of Epidemic Cerebrospinal Meningitis. *J. Med. Research* 14: 59, 1905.
5. Duval, Charles W.: Septicemia with Acute Fibrino-purulent Pericarditis and Hypopyon Iritis Caused by the Meningococcus. *J. Med. Research* 19: 255, 1908.
6. Herrick, W. W.: Meningococcic Pericarditis. *M. Clin. North America* 2: 411, 1918.
7. Zaccaria: Meningococcemia-Meningite Cerebrospinale (Pericardite Meningococcica?). *Polidinico (sez. Med.)* 36: 220, 1929.
8. Trace, I. M. and Berkovitz, Charles: Meningococcic Purulent Pericarditis Complicating Epidemic Cerebrospinal Meningitis. *J. A. M. A.* 97: 246, 1931.
9. Saphir, O.: Meningococcus Myocarditis. *Am. J. Path.* 12: 677, 1936.
10. Adshad, G. P.: The Treatment of Cerebro-spinal Meningitis by Antimeningococcus Serum at the Royal Naval Hospital, Haslar, 1915-16-17. *Med. Res. Council Special Report Series No. 17*: 59, 1918.
11. Holm, M. L. and Davison, W. C.: Meningococcus Pneumonia. I. The Occurrence of Post-Influenza Pneumonia in which the *Diplococcus Intracellularis Meningitidis* Was Isolated. *Bull. Johns Hopkins Hosp.* 30: 324, 1919.
12. Master, Arthur M.: Meningococcemia with Endocarditis. *J. A. M. A.* 96: 164, 1931.
13. Winslow, Nathan and Shipley, A. M.: Pericardiectomy for Pericardium. *Arch. Surg.* 15: 317, 1927.
14. Camp, P. D. and White, P. D.: Pericardial Effusion: A Clinical Study. *Am. J. M. Sc.* 184: 792, 1932.
15. Shipley, A. M. and Winslow, Nathan: Purulent Pericarditis. *Arch. Surg.* 31: 375, 1935.
16. Carbone, Arturo and Campbell, E. P.: Prolonged Meningococcemia. *Arch. Int. Med.* 61: 646, 1938.
17. White, P. D.: Heart Disease. New York, 1937, The Macmillan Co., Second Edition.
18. Levine, S. A.: Clinical Heart Disease. Philadelphia, 1938, W. B. Saunders Co.
19. Morgan, Hugh J.: Chronic Meningococcus Septicemia. *Bull. Johns Hopkins Hosp.* 32: 245, 1921.

Department of Reviews and Abstracts

Selected Abstracts

Katz, L. N., and Lindner, E.: Quantitative Relation Between Reactive Hyperemia and the Myocardial Ischemia Which It Follows. *Am. J. Physiol.* 126: 283, 1939.

The quantitative effect on coronary flow of different periods of myocardial ischemia was observed in an isolated preparation of the dog heart with ventricles fibrillating. Blood flow through the forelimb of the same animals was studied simultaneously under the same conditions. In this preparation coronary flow is determined entirely by active changes in the coronary vessels.

In the heart, correlation of the components of the ischemic periods, with those of the subsequent hyperemic periods and analysis of the relationships found, led to the following conclusions:

1. In this preparation, the coronary blood supply is greater than that necessary to meet myocardial needs.

2. The hyperemia due to the ischemia is more than adequate to make up for the myocardial deficit acquired.

3. The cause of the hyperemia seems to be an easily diffusible dilator substance which is eliminated in the presence of oxygen.

4. The degree of hyperemia not only varies with the duration of the ischemia and hence with the accumulation of the dilator substance, but also with the responsiveness of the coronary vessels to this substance.

The coronary vessels are decidedly more reactive to ischemia than are the limb vessels.

The importance of reactive hyperemia as a mechanism operating to compensate for any inadequacies in coronary flow in the intact animal is emphasized, and the bearing of these data on reactive hyperemia in other vascular beds is suggested.

AUTHORS.

Christianson, Oscar O.: Observations on Lesions Produced in Arteries of Dogs by Injection of Lipids. *Arch. Path.* 27: 1011, 1939.

Lesions were produced in arteries of dogs by injecting into the media of the abdominal aorta and femoral arteries, human fat alone or mixed with fatty acids, calcium soaps, or cholesterol. The severity and chronicity of the lesions varied with the acidity and speed of dispersal of the fat mixture. Human fat and fatty acids produced marked acute inflammatory lesions which healed rapidly because the lipids absorbed readily. Human fat mixed with calcium soaps or cholesterol was absorbed slowly and caused a chronic lesion. In the formation of arteriosclerotic lesions in man the infiltrating lipids as well as cholesterol may be important in producing fibrous tissue.

Most of the medial lesions produced disruption or splitting of the internal elastic lamina and development of intimal plaques. Thus intimal lesions were secondary to medial lesions simulating the early changes described in arteriosclerosis in man. Injuries of the media may be important in the production of secondary intimal changes which predispose to the deposition of lipids in the early lesions of arteriosclerosis.

NAIDE.

Hallock, Phillip: Lactic Acid Production During Rest and After Exercise in Subjects With Various Types of Heart Disease, With Special Reference to Congenital Heart Disease. *J. Clin. Investigation* 18: 335, 1939.

An increased concentration of lactic acid in the venous blood is evidence of an inadequate supply of oxygen to the tissues.

There is only a slight increase of lactic acid in the blood following mild exercise in normal individuals, an average increase of about 2 mg. per 100 c.c. of blood above the resting value. The normal upper limit of concentration of venous blood lactic acid following our exercise test did not exceed 21 mg. per 100 c.c. of blood.

The blood lactic acid studies show that tissue anoxia is not present at rest in patients with congenital heart disease, either in the presence or absence of cyanosis.

Following mild exercise there is a definitely abnormal rise of blood lactic acid in the cyanotic group of congenital heart disease, indicating a greater liability to the development of tissue oxygen deficit after even slight physical exertion.

The presence of cyanosis and polycythemia in congenital heart disease does not necessarily indicate that oxygen deficit will develop following mild exertion for no significant rise of lactic acid level occurred in a case of morbus caeruleus.

Following mild exertion, a definitely abnormal rise may occur in some acyanotic cases of congenital heart disease, but the rise is not as great on the average as in the cyanotic group.

When dyspnea follows mild exercise the presence of tissue oxygen want may be assumed to be present regardless of what specific cardiac defect is ultimately responsible.

AUTHOR.

Gubner, Richard, Schnur, Sidney, and Crawford, Hamilton: The Use of CO₂ Inhalation as a Test of Circulation Time. *J. Clin. Investigation* 18: 395, 1939.

CO₂ inhalation may be employed clinically to estimate circulation time. The CO₂ test measures "left heart" time (lung to respiratory center). Its advantages are that it is a physiologic respiratory stimulant; it is entirely harmless; the effect is transitory; it does not require injection, and it may be used repeatedly in the same subject.

The circulation time, by this method, is prolonged in heart disease commensurate with the degree of left heart failure. Normal values range from 5 to 10 seconds and correspond closely to the expected results according to the cyanide and ether times.

AUTHORS.

Gold, Harry, Kwit, Nathaniel T., Otto, Harold, and Fox, Theodore: On Vagal and Extravagal Factors in Cardiac Slowing by Digitalis in Patients With Auricular Fibrillation. *J. Clin. Investigation* 18: 429, 1939.

There is no general agreement regarding the role of the vagus in the ventricular slowing by digitalis, some maintaining that the drug acts mainly on conduction directly, and others, that its action is mediated chiefly or wholly through the vagus.

In the present investigation on patients with auricular fibrillation the authors found, as others have, that paralytic doses of atropine always cause some acceleration of the ventricle which has been slowed by digitalis, and that this effect varies from slight acceleration to complete abolition of the slowing.

They have observed, however, that if the doses of digitalis are large enough, atropine cannot prevent digitalis from producing marked slowing of a rapid ventricle (to 100 a minute or slower).

In digitalized patients with auricular fibrillation, the ventricle is maintained at a slow rate usually by the summation of two factors: one, a vagal factor (abolished by atropine), and two, an extravagal factor (not abolished by atropine).

In the average case, the vagal factor predominates in the slowing of the ventricle after moderate doses of digitalis, while the extravagal factor predominates after large doses.

Which of the two factors (vagal or extravagal) will dominate in the control of the slowed heart rate depends, therefore, upon the degree of digitalization. Contrary to statements found in the literature, the results show that it is not a matter of individual peculiarity, the degree of heart failure, or the length of time the heart has been under the influence of digitalis.

The discordant views in the literature regarding the role of the vagus and the factors which alter its role, in slowing of the ventricle in auricular fibrillation, arise from the failure to make adequate observations on the effect of maximum doses of atropine after different doses of digitalis in one and the same subject.

AUTHORS.

McMichael, John: Hyperpnea in Heart Failure. Clin. Sc. 4: 19, 1939.

The best available method of standardizing measurements of pulmonary ventilation is by the use of a ventilation equivalent. The ventilation equivalent for oxygen is liable to a considerable error, especially with fluctuations in the respiratory quotient. The ventilation equivalent for CO_2 is less liable to fortuitous changes. Normal values of these functions are surveyed statistically.

The standard error of the acetylene method of determining cardiac output is assessed as 4.5 per cent from 85 checked determinations.

In heart failure there is no great correlation between hyperpnea and vital capacity. There is, however, a close correlation between cardiac output and hyperpnea.

When the general systemic blood flow is lowered in cardiac failure, there is good reason to believe that the cerebral blood flow is not depressed to the same degree.

Consideration of published and personal data on the jugular venous oxygen content supports the hypothesis that the cerebral blood flow is subnormal in hyperpneic cardiac subjects.

AUTHOR.

De Boer, S.: Researches on the Electrocardiogram. Cardiologia 2: 202, 1938.

A polemical review of the author's work is assembled in order to refute Lewis' theory of limited potential differences and also Craib's deductions regarding monophasic curves. The author advocates the interference theory.

KATZ.

Burger, R.: The Electrical Field of the Heart. Cardiologia 3: 56, 1939.

A lead can be taken from the surface of the body as a whole using the metal tub bath with a metal lead as the W electrode (bath electrode), and using this as an indifferent electrode. This was employed in five normal cases. It was found that the decrease due to the short-circuiting effect of the water on the potential

differences of the extremity leads was a constant percentage at different instances of the cardiac cycle. This method is used to deal at great length with the question of what is an "indifferent electrode," a "zero-potential electrode," and a "unipolar lead."

KATZ.

Burger, R., and Wuhrmann, F.: The Electrical Field of the Heart. Cardiolgia 3: 139, 1939.

A method is suggested of determining the electrical field of the heart at different instants of the heart cycle. Such diagrams are called diagrams of potential differences. These are obtained by measuring the potential at a particular instant in the heart cycle of many points in the body especially on the precordium, back, and in the esophagus. A relatively complex mathematical derivation is used. Comparison made by this means and by the vector diagram ordinarily used shows that the location and movements of potentials can be followed more accurately by the authors' methods especially since their method gives the individual components of the electrical field and not only the resultant.

KATZ.

Cowan, John: Some Disturbances of the Rhythm of the Heart. Brit. Heart J. 1: 3, 1939.

Alterations in the rhythm of the heart, as isolated signs, are not necessarily of serious significance.

James Mackenzie stated (1912) that *sinus irregularity* in a healthy individual was a normal occurrence, and many observers have subsequently confirmed the accuracy of his dictum. It is true that *sinoauricular block* may, as shown in some of the cases which we have collected, be accompanied by serious symptoms, but the subsequent history of these patients shows that, in the absence of signs of cardiac disease, the prognosis from the cardiac standpoint is quite good. Any danger lies in the nature of the nervous disorder which occasions it.

The occurrence of *extrasystoles*, *per se*, has not any sinister significance. It is true that if they recur rapidly for long periods the mere rapidity of the cardiac contractions may produce cardiac failure, but, in the absence of signs of cardiac disease, any cardiac symptoms rapidly pass as soon as the normal rhythm is restored. A man, who died from paralysis agitans at the age of 75, had been liable to attacks of paroxysmal tachycardia from the age of 18 and had lived a very strenuous life for many years.

The prognosis in cases of *nodal rhythm* depends, as in sinus irregularity, upon the nature of its cause. The outlook is serious if it is due to myocardial lesions, but good if it is due to nervous causes.

The occurrence of *auricular fibrillation* is generally a signal of impending danger, but the exceptions to the rule are fairly numerous. Cases have been reported where the arrhythmia persisted for ten or even twenty years. One of my patients bore a child safely although her auricles had been in fibrillation for at least three years. The irregularity is not the important factor in the failure. The danger lies in the frequency of the ventricular contractions or in the continued activity of the cause of the irregularity. Fibrillation may be due to several causes; pathologic lesions in the auricular muscle, of chronic or acute character; autointoxications, as in Graves' disease; poisons introduced from without (digitalis, anesthetics, coal-gas poisoning, etc.); physical stresses; and perhaps to disturbances of the nervous control of the heart (Cowan, 1929). The cause may be permanently or temporarily in action. The prognosis follows the cause.

Heart block and bundle branch block repeat the story. As they are most frequently due to myocardial disease the prognosis is, as a rule, serious, but many patients live in fair health for many years. Again the danger lies in the rate of the ventricular contractions, or in the character of the process which has disturbed the rhythm of the heart.

AUTHOR.

Peel, A. A. Fitzgerald: *The Significance of Electrocardiograms Showing a "Second Positive Wave of QRS" in Lead III.* Brit. Heart J. 1: 86, 1939.

Organic heart disease is more common in patients whose electrocardiograms show a "second positive wave of QRS_2 " than in the material from which these cases were collected (82 against 72 per cent). Many of these electrocardiograms show some other significant abnormality, in which case organic disease is always present, and the mortality since 1928 to 1933 has been 90 per cent.

Organic lesions are much more frequent in patients whose sole electrocardiographic abnormality consists of a "second positive wave of QRS_2 " than in patients whose electrocardiograms are completely normal (70 per cent against 43 per cent). The increase is due to a greater number with coronary disease, hypertension, or arteriosclerosis (42 per cent against 8 per cent).

Where it has been possible to fix the time of appearance of the "second positive wave of QRS_2 ," this has occurred when an active pathologic process was affecting the myocardium. In seven out of eight cases in which it ultimately disappeared, the patient's capacity for effort improved, at least temporarily.

When a "second positive wave of QRS_2 " is the only electrocardiographic abnormality, the shape of the complex is important for diagnosis and prognosis, and its breadth gives further assistance in prognosis.

As regards the shape of the complex, the height of the initial R is the determining factor. When this was prominent, deflection exceeding 2 mm. in height, organic disease was always present; and the mortality in cases with an otherwise normal electrocardiogram was 50 per cent. When the initial R was a small deflection of less than 2 mm. in height, the incidence of recognizable organic disease was only 62 per cent, and the mortality in cases with an otherwise normal electrocardiogram was only 12 per cent.

The breadth of QRS gives little help in diagnosis, but is of great importance in prognosis. The mortality rises steadily from 22 per cent with a QRS below 0.08 sec., to 55 per cent at 0.08 sec., and to 72 per cent above 0.08 sec. These mortality figures are almost identical with those found in healing with another series of electrocardiograms where the abnormality was a "large Q_s ." The significance of the breadth of QRS, therefore, appears to be independent of the nature of any abnormality which may be present.

AUTHOR.

Chamberlain, E. Noble, and Hay, J. Duncan: *The Normal Electrocardiogram.* Brit. Heart J. 1: 105, 1939.

To determine the limits of physiologic variation in the electrocardiogram and any changes that might occur with age, 302 normal subjects have been investigated. Each was subjected to a rigorous examination, including blood pressure readings and Wassermann reaction. The following points are deemed worthy of emphasis.

The P wave was often flat or scarcely perceptible in Lead I and occasionally had a split or broad summit. A few examples of inversion P_s were seen.

The R wave varied within wide limits in its amplitude, and slight notching of the descending limb was not uncommon.

The S wave, although usually well defined, may slope gradually into the R-T segment.

True S-T deviation was so rare and so minute that it must be regarded with great suspicion, but peculiarities in the formation of the S-T interval were very common and must not be confused with genuine S-T deviation.

Slight degrees of notching and of low voltage in the QRS complex in Leads I and II were not common. The types of record found can be seen better by inspection of the illustrations than by description.

Right axis deviation in a pronounced form was uncommon even in young persons, while left axis deviation occurred quite frequently at all ages, increasingly so in the later decades where it was found in one-sixth of all cases.

Inversion of T was never found in Lead I, but inversion of T in both Leads II and III was present in four cases. The former must be considered as pathologic whenever it occurs, and the latter as suspicious. Inversion of T in Lead III only was present in 29 per cent of the total 302 cases, and considerable variation in the shape of the wave was recognized.

The only unusual finding as regards time intervals was the occurrence of a few cases where the P-R interval was 0.22 second.

Age variations were slight, the most important being an increase in the left axis deviation in the later decades of life.

AUTHORS.

Wood, Paul, and Selzer, A.: A New Sign of Left Ventricular Failure. *Brit. Heart J.* 1: 51. 1939.

A widened P wave of low voltage, usually bifid or flat-topped, has been found in association with left ventricular failure in cases of hypertensive heart disease and of aortic incompetence.

It is suggested that this P wave results from left auricular stress.

AUTHORS.

Bruetsch, Walter L.: The Histopathology of the Psychoses With Subacute Bacterial and Chronic Verrucose Rheumatic Endocarditis. *Am. J. Psychiat.* 95: 335. 1938.

The involvement of the brain during the course of an endocarditis is not uncommon. From an etiologic point of view two types of psychosis with endocarditis can be distinguished.

(1) Psychoses with subacute bacterial endocarditis, terminating fatally within several months. Histologic examination reveals numerous miliary abscesses and masses of cocci in capillaries of the brain cortex and in other organs.

(2) Psychoses with chronic rheumatic endocarditis. The patients in this group may present any reaction type. Some of the cases were diagnosed as dementia praecox, other cases as manic-depressive or involutional psychoses. A 62-year-old patient with a recent rheumatic infarction of the parietal-occipital region was classified as senile psychosis.

The anatomic findings in the brain consisted of small or large areas of infarction, being usually the result of rheumatic-endarteritic changes. Or the brain was grossly normal, but microscopic examination disclosed numerous acellular areas, an occasional granuloma, and small connective tissue scars. In one patient with a psychosis of short duration a rheumatic encephalitis was present.

AUTHOR.

Bruetsch, Walter L.: Chronic Rheumatic Brain Disease as a Cause of Mental Disorders. *Ztschr. f. d. ges. Neurol. u. Psychiat.* 166: 4, 1939.

The material on which this work is based comprises 475 complete autopsies, performed in an institution for mental diseases, in which particular attention was given to the presence of rheumatic valvular heart disease. The frequency of chronic rheumatic endocarditis among mental patients is given as 4 per cent. This finding is of particular interest, since obvious rheumatic manifestations, in particular polyarthritic symptoms, are rarely seen in mental hospitals. Histologic examination of all the organs of these patients revealed the interesting fact that the long-continued rheumatic infection had not only involved the heart, but also the brain and other organs, such as kidneys, spleen, pancreas.

The fundamental rheumatic lesion in the brain consisted of a vascular process of an obliterating endarteritic type with subsequent degeneration in the parenchyma. The anatomic findings seem to suggest that in a great majority of mental patients with chronic rheumatic valvular disease, a rheumatic brain involvement may be present.

The relation of rheumatic infection to arterial disease was first emphasized by Krehl who described in 1890 rheumatic endarteritis of the small myocardial arteries. In more recent years (1926) von Glahn and Pappenheimer and others demonstrated specific rheumatic lesions in the vessels of all the internal organs. They found rheumatic-endarteritic changes in the lungs, kidneys, pancreas, ovaries, and testes. If in this process the cerebral vessels take part, changes in the nervous parenchyma will occur. For this condition the term of chronic rheumatic brain disease was used.

AUTHOR.

Gross, Harry, and Handler, Bernard J.: Sclerosis of the Superior Vena Cava in Chronic Congestive Heart Failure. *Arch. Path.* 28: 22, 1939.

The superior venae cavae of twenty-one persons showing chronic congestive heart failure were studied and compared with those of a group showing hypertrophy of the right side of the heart without failure and with those of another group in whom there was no cardiac lesion at all.

In persons with chronic congestive heart failure associated with increased tension in the right side of the heart and in the superior vena cava, sclerosis of the superior vena cava is a common finding.

Histologically, the sclerotic process in the superior vena cava is characterized by hypertrophy of all the coats of the vein, most marked in the muscular layer of the media. These alterations are thickening and scarring of the intima, splitting and reduplication of the internal elastic membrane, and widening of the media with hypertrophy of the muscle cells and increase of collagen. Eventually, from increased tension and impairment of nutrition, fragmentation, and replacement of muscle fibers occur.

Involvement of the superior venae cavae in persons not having congestive heart failure was slight and infrequent, and in not a single vein were all the coats of the vessel involved. Medial hypertrophy, which was so constant and marked in the superior venae cavae of the group who died in congestive heart failure, was an infrequent occurrence.

Phlebosclerosis and arteriosclerosis are similar in morbid anatomy and pathogenesis. The pathogenesis of sclerosis of the superior vena cava appears to be prolonged increase of intravascular pressure.

AUTHORS.

Jones, Noble W., and Rogers, Arthur L.: Chronic Infection and Atherosclerosis. *Med. J. Australia* 1: 851, 1939.

The observation that compensation could not be restored in two patients with congestive heart failure until tonsillectomy and radical sinus surgery was performed in one patient and drainage of infection in the common bile duct in the other, led the authors to make special histologic and bacteriologic studies of the arteries in the first patient and subsequently in other atherosclerotic patients. In the sinus tissue of the first patient the arterioles lying in the depth of the membranes were noteworthy because of an almost universal subacute arteritis and a thrombotic process which occluded many of their lumina. Scattered diffusely throughout the walls of the vessels, and in the thrombi also, were many microorganisms in the form of diplococci, as revealed by specially stained sections. This picture was at marked variance with the arterioles in the sinus tissues removed from patients suffering from chronic arthritis or asthma, in which the blood vessels were slightly or not at all affected. The arteries in the walls of gall bladders removed from atherosclerotic patients were found to be in an inflammatory state, with diplococci present in the involved areas.

These facts suggested a relationship to distant thromboses and led the authors to study eleven unselected patients who died from acute coronary thrombosis. In all, the same general histologic picture of subacute arteritis with atheromatous degeneration was noted, and also in each one microorganisms in the form of diplococci were found in the tissues. In a few instances single and short chain cocci were seen. In these eleven cases there were associated chronic cholecystitis three times and a severe grade of pericemental infection and chronic sinus disease each twice.

The coronary arteries of children and patients with essential hypertension did not reveal any inflammatory changes, nor could microorganisms be found in them.

The inflammatory reaction and diplococci were demonstrated in the arterial wall of arteries in one patient with thromboangiitis obliterans and in a patient with periarteritis nodosa.

In conclusion the authors point out that in certain instances of atherosclerotic heart disease there exists a clinical relation to infection and that the removal of the latter beneficially affects the course of the former. In addition they were able to demonstrate microorganisms in the walls of all atherosclerotic vessels in which a careful search was made.

NAIDE.

Stead, Eugene A., Jr., and Kunkel, Paul: Mechanism of the Arterial Hypertension Induced by Paredrinol (*a*-N-Dimethyl-p-Hydroxyphenethylamine). *J. Clin. Investigation* 18: 439, 1939.

Paredrinol (*a*-N-dimethyl-p-hydroxyphenethylamine) produces in normal subjects a type of acute arterial hypertension that closely resembles that observed in disease. The tendency to a slower heart rate, the vigorous apex impulse, the loud heart sounds, and the hypertension itself are the only outstanding abnormalities produced by the administration of the drug.

This hypertension differs greatly from that produced by epinephrine.

The arterial blood pressure response in different subjects, and in the same subject on different days, varies greatly. The average duration of the hypertension after the intramuscular injection of 25 mg. of paredrinol is one hour.

The blood flow in the dilated hand is moderately decreased. The spontaneous fluctuations in vasomotor tone in the hand and foot are decreased. The venous tone in the hand is increased. The venous pressure is increased by from 30 to

40 mm. of water. The T waves in the electrocardiogram become higher. These changes are usually not great enough to be detectable unless the resting values for the particular subject are known.

There is no significant change in blood flow in the foot, forearm, and calf. The cardiac output, circulation time, and basal metabolism are not significantly altered.

The decrease in heart rate results from an increase in vagal tone brought about by stimulation of the carotid sinus and aortic nerves, since if the vagal effect is removed by atropine, paredrinol causes an increase rather than a decrease in heart rate. When atropine is given before the injection of paredrinol the arterial pressure, particularly the diastolic, rises to higher levels than after paredrinol alone.

The combination of nitrite and tilting to the upright position pools sufficient blood to reduce the paredrinol hypertension to normal. Thus, if the arterial blood pressure rises to alarming heights, or if headache develops, the hypertension can be rapidly and permanently reduced.

The peripheral blood flow in subjects with arteriosclerosis and in subjects who have had a preganglionic sympathectomy is not increased by raising the arterial pressure head with paredrinol.

The hypertension produced by paredrinol may result from either or both of the following mechanisms: 1. A primary increase in peripheral resistance from a direct vasoconstrictor effect on the minute vessels (arterioles, capillaries, venules); 2. A primary increase in venous tone and an emptying of the splanchnic reservoirs, causing increased venous return to the heart and a secondary increase in peripheral resistance.

AUTHORS.

Katz, L. N., and Jochim, K.: Observations on the Innervation of the Coronary Vessels of the Dog. *Am. J. Physiol.* 126: 395, 1939.

A method is described for determining the action of the sympathetic and parasympathetic nerves on the caliber of the coronary blood vessels in a preparation consisting of an isolated head and heart with fibrillating ventricles.

Evidence is presented showing that in the dog:

1. The vagi carry only cholinergic coronary vasodilator fibers which are tonically active. No evidence was obtained of cholinergic coronary vasoconstrictor fibers.
2. The stellate ganglia send to the heart adrenergic coronary dilator and adrenergic coronary constrictor fibers, both of which are tonically active.
3. The tonic action of the sympathetic nerves is predominantly vasoconstriction.

AUTHORS.

Perlow, Samuel, and Halpern, S. Sherman: Surgical Relief of Pain Due to Circulatory Disturbances of the Feet. *Am. J. Surg.* 45: 104, 1939.

Operative peripheral nerve block has been a satisfactory method of relieving pain in many patients with peripheral vascular disease. However, occasional sloughing ulcers occur at the site of incision and in some cases the poor circulation causes the surgeon to hesitate to perform nerve block. In a search for another simple pain-relieving measure, it was found that injection of procaine in oil solutions into peripheral nerves induced anesthesia for one to forty days. Anesthesia involved the sympathetic, sensory, and motor fibers. No harmful results were produced by the procaine in oil injection into the nerve. The anesthesia is similar to that obtained by peripheral nerve block with alcohol or crushing but is not so long lasting. However, it can be repeated as desired and has the advantage of not requiring an operative incision.

NAIDE.

Book Reviews

ATLAS DE PHONOCARDIOGRAPHIE CLINIQUE: By A. Calô, Assistant étranger à la Faculté de Médecine de Paris. Membre correspondant étranger de la Société Française de Cardiologie. 104 pages, 150 illustrations, 60 francs, Paris, 1938. Masson et Cie, Editeurs, Libraires de L'Académie de Médecine, 120 Boulevard Saint Germain, Paris, France.

During the last few years there has been a great revival of interest in the graphic registration of heart sounds and murmurs, with the result that several makers of electrocardiographs have placed on the market apparatus for recording a sound tracing simultaneously with an electrocardiogram. Many physicians have not found the records as useful as they had anticipated, however, largely because they do not know how to interpret the graphs. For this reason a book that contains a large number of sound records and describes their salient features is to be welcomed.

This atlas opens with a brief discussion of the method employed and the technique required to obtain tracings free of unwanted vibrations. This is followed by classification into logical groups of the different sounds and murmurs arising from the heart, and a fairly detailed discussion concerning their origin, time of occurrence in the heart cycle, duration, and other important characteristics.

The second part of the atlas, which occupies three-quarters of the book, is devoted to the reproduction and description of sound records from a large group of patients, including several with normal heart sounds. Tracings that illustrate the common murmurs encountered in patients with valvular heart disease and congenital heart disease are shown, in addition to many other graphs depicting alterations in the heart sounds and various types of gallop sounds. The presentation is very complete because in each instance sound tracings from at least three points on the chest, i.e., the cardiac apex and the aortic and pulmonic areas, are shown, and each sound record is taken simultaneously with one lead of the standard electrocardiogram. The majority of graphs also include a simultaneous arterial pulse tracing. On the page opposite the graphic records, the author gives a brief summary of the history and physical examination of the patient whose records are shown, together with an orthodiagram and an interpretation of the standard electrocardiogram and the sound tracings.

The tracings are very well reproduced throughout the atlas, and, although very low frequency oscillations seem to dominate many of the records, these vibrations are seen to occur quite constantly in every heart cycle, indicating that they are not artifacts. The author emphasizes that many of the low frequency vibrations that appear on the records would be heard with difficulty, or might be entirely inaudible. Attempts are made to estimate from the tracings the fundamental frequency in the heart sounds and murmurs. The reviewer does not feel that such frequency determinations are worth while, because the results obtained depend to a very large degree on the nature of the microphone and amplifier employed in the recording system.

An excellent bibliography is provided, and the atlas should be of great value to many physicians desiring information on this subject.

FRANKLIN D. JOHNSTON.

CARDIOVASCULAR DISEASE IN GENERAL PRACTICE: By Terrence East, M.A., M.D., F.R.C.P. (London), Physician and Physician in Charge of Cardiological Department, King's College Hospital, London. 206 pages, 43 illustrations, \$3.50, 1939, H. K. Lewis and Co.

This book of approximately two hundred pages is an extremely useful summary of the knowledge relating to heart disease that is most essential for the general practitioner, or indeed for the specialist in this field. It might be more accurately entitled "Heart Disease in General Practice," inasmuch as only one short chapter is devoted to vascular diseases; the three selected for discussion are thromboangiitis, Mönckeberg's sclerosis, and Raynaud's syndrome. It is probably true in England, as it is in the United States, that very few "heart specialists" are also specialists in the field of peripheral vascular diseases, and this volume accurately reflects the extent of knowledge and interest of the average cardiologist.

There are chapters upon all the conventional aspects of heart disease, and the author's classifications with reference to etiology, functional state, and anatomic changes are those now generally approved by most authorities. His discussion of etiologic factors such as rheumatic fever, syphilis, and hypertension is very sound, and seems to include all important recent contributions with the single exception of the surgical treatment of hypertension, which he probably regards as still of unproved value. The chapters dealing with congestive heart failure, anginal heart failure (here designated "failure of the coronary circulation"), failure of the peripheral circulation, and the treatment of these conditions, are among the best in the book, and are worthy of praise. There is a long chapter dealing with the cardiovascular system in anemia, chronic pulmonary disease, chronic renal disease, minor infections, anesthesia, pregnancy, and athletics, and it would be well if all practitioners could be thoroughly familiar with the sane comments contained therein.

Obviously, the author has aimed at presenting in rather brief and authoritative form the most important aspects of current knowledge in this field, in so far as these are useful in the diagnosis of disease and treatment of patients by the practitioner. He has succeeded extraordinarily well. One is constantly impressed by his wide knowledge of recent literature, his ability to summarize broad topics in a few sentences, and especially by his sane judgment, which is obviously based on extensive experience. There are very few statements in the book to which one can take exception, and these are of minor importance. It is a pleasure to commend it without reservation.

H. M. MARVIN.

RHEUMATISCHE KREISLAUSCHÄDIGUNGEN: By Oberarzt Dozent Dr. Siegfried Dietrich, II Med. Univ.-Klinik Berlin, with a foreword by Professor Dr. G. von Bergmann. 178 pages, 34 illustrations, 1938, Theodor Steinkopff, Dresden and Leipzig.

This is volume 7 of the system called *Der Rheumatismus*, edited by Professor Dr. Rudolf Jürgens. The monographs cover the entire field of rheumatic diseases. Dr. Jürgens explains in the editor's foreword the widespread prevalence and importance of the rheumatic diseases, the lack of understanding of their nature, and his ambitious and basically sound plan of bringing together all of the facts and newer contributions of investigators and teachers and the experiences of specially interested physicians. He aimed to include every important item that in any way might help in the solution of any of the many problems of rheumatism in all of its forms and hoped to treat thoroughly the recognition, pathogenesis, prophylaxis, pathology, clinical manifestations, and management and treatment of each type of rheumatic disease. Besides a consideration of pharmacologic agents, the natural

methods of healing, physical therapy, including helio-, electro-, hydro-, and balneo-therapy, gymnastics, massage, and climatic management, discussions by eminent physicians and investigators were to be emphasized. It was planned to make each monograph complete in itself.

In a foreword to this volume, Prof. Dr. G. von Bergmann points out that Dietrich's monograph is the outgrowth of the traditional interest of the members of his clinic in the whole subject, to the practical knowledge of which many contributions had been made by his predecessors. He points out that the newer conceptions of the German rheumatism clinic which are set forth by Dietrich are most significant.

Dietrich's monograph fulfills the editor's expectations. He separates rheumatic fever from infectious arthritis and agrees with the English and American workers that the carditis should be regarded as the chief manifestation of the disease, while the polyarthritis, chorea, and other symptoms are complications. Dietrich states that fresh rheumatic pancarditis or acute inflammatory rheumatism may be the first act of the tragedy, which is rarely completed in a single act, and usually returns in the form of carditis. The seriousness of this situation is duly emphasized as a problem of social medicine, since two-thirds of the afflicted persons, most of whom are youths, succumb or become total invalids within fifteen years. In Germany every fourth death is due to heart disease, and 31 per cent of all invalided males were suffering from disease of the circulatory system. The social welfare attitude that the author emphasizes seems justified. The work of the English and our own New England group of workers has been substantiated. The author has a thorough knowledge of the literature and has had broad clinical experience. His contribution is worthy of study and should be a source of much help and some encouragement to those working in this important field. He hopes that prophylaxis by increasing resistance to infection will decrease the destruction that is being wrought by rheumatic fever.

GEORGE HERRMANN.

ELEMENTS DE PHYSIOLOGIE CLINIQUE DE L'APPAREIL CIRCULATOIRE (Essentials of Clinical Physiology of the Circulatory Apparatus): By J. Castaigne and P. Dodel. Masson et Cie, Paris, 1939, 143 pages, 81 illustrations, price 27 fr.

A pocket-size book giving the information on the circulation found in most textbooks of physiology, with special emphasis on its clinical importance and relationships.

ISAAC STARR.

DIE PERIPHEREN DURCHBLUTUNGSSTÖRUNGEN (MEDIZINISCHE PRAXIS, BAND 27): By Dr. med. habil. M. Ratschow, Dozent für innere Medizin a. d. Martin-Luther-Universität Halle, a. S. 193 pages, 46 illustrations, 1939, Theodor Steinkopff, Dresden and Leipzig.

The purpose of this twenty-seventh monograph of the series of Medical Reviews entitled "Medizinische Praxis" is, according to the introduction by Cobet, to fill the gap in the German literature which was filled in the English by Sir Thomas Lewis' book on peripheral vessels, and to collect and interpret in German those facts learned about the peripheral circulation during the last ten years which have a clinical bearing.

The introduction (six pages) limits "peripheral disturbances in blood flow" to local phenomena, as opposed to cardiac failure. Thus the role of the minute vessels in local allergy, but not in anaphylactic or traumatic shock, comes in for discussion. A historical note, perhaps necessarily brief and incomplete, follows. The

next section (ten pages), entitled "Structure, Function, and Interplay of the Peripheral Vessels," is devoted almost entirely to function. The description is formal, and so brief as to be useful only in outlining the methods of vascular regulation for beginning students.

A discussion of the general characteristics of, and tests for, peripheral vascular disturbance occupies the next forty pages. Pain on exercise he believes is the "cry of the tissues for oxygen." He does not discuss Lewis' work concerning a special substance as a cause of pain, but cites Brown and Allen as having shown, by novocainization, that arterial spasm can interfere markedly with local circulation. Rest pain is more complicated; besides marked reduction of the circulation, he believes neuritis may be a frequent cause, and that it may be distinguished from pain due to "pre necrotic states" by failure to relieve it by increasing venous pressure. In describing a work test for pain, the interesting fact is brought out that by elevating the leg a difference between the old and the young as regards appearance of pain can be demonstrated.

There follows a short discussion of the physiologic significance of color changes in the skin with changes in environmental temperature and position. Considerable space is devoted to the meaning of surface temperature and its measurement. Discussing only well-known facts, he points out that normal surface temperature may occur in the presence of well-marked narrowing of large arteries, and, therefore, advocates the usual tests of function by direct and reflex heating or cooling of the region to be tested, and by nerve block combined with temperature measurements to distinguish functional from organic arterial disease. Only a passing statement is made concerning oscillometry and plethysmography, which methods, he says, in Germany are relegated solely to "scientific" use, but appear to have been used clinically to advantage in America.

Reactive hyperemia, which he places under the heading, "Disturbances of the Ability of the Peripheral Vessels to Dilate," is adequately treated. He leans to the view that reactive hyperemia is, as Lewis believes, probably due to the liberation in the tissues of more than one substance, and in so doing he embraces the notion of O. Muller that it may in part be the result of nervous influences. His apparatus for interrupting arterial circulation is described in detail, and he finds that study of reactive hyperemia is useful in distinguishing between certain vascular disorders, as follows:

1. *Delayed* appearance with *diffuse* development of *full* color means complete occlusion of a large artery with good collateral circulation.
2. *Delayed* appearance with *diffuse faint* color means that narrowing of the finer vessels (arteriosclerosis, for example) is present.
3. *Delayed* appearance with *marked mottling* is indicative of very severe curtailment of the blood supply and is usually seen in endarteritis obliterans.
4. *Prompt* appearance with *good* color which disappears *quickly* suggests the angiospastic diseases (Raynaud's).
5. *Prompt* appearance with *deep* color which disappears *very slowly* suggests acrocyanosis.

The next chapter (fourteen pages) is given over to direct methods for study of vessels, of which there seem to be two, namely, capillary microscopy and angiography (roentgenography of arteries and veins after injection of contrast media). For estimation of the circulation he recommends capillary counts and F. Lange's test, namely, the time required for the flow of blood in the capillaries to cease after occlusion of the circulation.

The discussion of angiography is full and interesting. The author makes several points: (1) the extent of collateral circulation can be accurately ascertained. (2) If the shadow of the lumen of a vessel ends in a point, the oc-

clusion is probably spastic; if blunt and transverse, probably organic in nature. (3) Corkscrew course and irregular width of lumen suggest arteriosclerosis; straight course and diffuse narrowing suggest endarteritis. (4) In prognosis of the life of an extremity, radiographic measurement of the length of time necessary for the veins to empty after arterial injection is important. (5) Valuable information may be obtained as to whether varices are due to obstruction of the deep veins or to failure of the valves of the communicating veins. Many reproductions of good roentgenograms accompany the text and illustrate these points. As a contrast medium the author prefers thorotrast (thorium dioxide) to the iodine-containing compounds such as Uroselectan, because the injection is unaccompanied by pain, and because he believes that the basic studies of von Lohr and the experiences of "the whole world" have now shown that the complications which follow its use are "trifling." His procedure is to shut off arterial circulation for five minutes prior to injection, in order to dilate the finer arterioles, and then to follow the course of the material after injection by serial roentgenograms.

The next section, a long one, is headed "Diseases Depending upon Disturbance of Blood Flow" (pages 73-136). A lengthy discussion concerning the nature and possible varieties of disturbance of flow enables the author to discard most of the older names for peripheral vascular diseases in his classification, and to set down simply several sorts of reaction. He concludes that "anders artige Reaktion Bereitschaft" means simply that subliminal stimuli take on vasomotor roles under certain circumstances.

His classification divides diseases into four main headings: (1) *Angiopathics*, or diseases resulting from an increased tendency of arteries either to constrict or to dilate, or to do both. In this category fall Raynaud's disease, ergotism, and erythromelalgia. (2) *Angiitides*, which include endarteritis obliterans, infectious arteritis, mechanical (physical) arteritis, such as frostbite, and phlebitis. (3) *Angioses*, i.e., degenerative lesions which include diabetic and senile arteriosclerosis and varicose veins. (4) *Occlusions* of arteries of any sort. External and internal causes of disturbances of the peripheral circulation are then briefly mentioned, namely, cold and moisture, nicotine, infections and endocrine disturbances (the list seems incomplete), and several pages of description of pathologic changes which take place in the arterial walls and tissue follow. Numerous good photomicrographs of various thrombotic processes are reproduced. Various diseases of the peripheral circulation are then described briefly under the headings given in this classification.

A short section is devoted to main points in diagnosis on a basis of signs and behavior with respect to the various functional tests, and a brief summary of how to localize occlusions from the character and site of pain is presented.

The next twenty-five pages (144 to 169) deal with treatment. After stating the aims of treatment, he sums up the general rules in seven "commandments": (1) Keep the extremities warm, (2) avoid injury and don't cut your own corns, (3) don't wear circular rubber garters, (4) don't cross your legs, (5) drink plenty of coffee and water, (6) avoid rich meats, and (7) don't smoke. The author recommends many of the usual forms of therapy, such as local and general heat, diathermy, nerve block, and reactive hyperemia. He tends to believe that just as good an effect on the circulation, if not a better, can be obtained from intermittent occlusion of the veins as from the various suction and pressure apparatuses. Nitrites, euphyllin, eupaverin, strychnine, and, especially, various preparations of theophyllin are useful. He finds that the various choline derivatives, acetyl- β -methylcholine chloride and carbaminoylcholin, have little effect, which is what he would expect from the rapidity of their destruction in the

body. Although he believes that it is too early to make categorical statements about the use of sex hormones, he feels sure that progynon has been beneficial in women and "testoviron," though less well tested, in man. He makes the statement that progynon can be used only in women, testoviron only in men.

In the treatment of necrosis and gangrene he puts bed rest first. Next comes treatment with warm carbon dioxide baths locally, as outlined by Cobet. Considerable space and emphasis are given to the use and good effects of this procedure in necrotic lesions. Of interest, too, is the emphasis which he puts upon the use of local infiltration of tissues with a solution of acetylcholine and 1 per cent novocaine solution. The extraordinary relief from pain obtained in this way is, to the author, very important, since it makes the use of narcotics unnecessary for hours at a time. He believes that the circulation to the tissues is also considerably enhanced by the presence of these drugs. The last step in treatment is the resort to surgery, and the indication for it is principally a rapid increase in the size of the gangrenous area under conservative treatment. Intra-arterial injection of contrast media to determine the site of amputation is a necessary preliminary.

The section on prognosis takes but half a page; it says little more than that most of the diseases under discussion are chronic, and that the prognosis is, in general, bad.

The monograph closes with eight pages devoted to the importance of testimony in connection with accident and invalid insurance. He notes the frequency with which the onset of symptoms follows an accident, but closes with a warning that, since even Raynaud's disease can be fatal, deflection of judgment in the clear distinction between accident and disease is not permissible.

It is a useful monograph but can hardly replace Sir Thomas Lewis' book.

J. MURRAY STEELE.

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*Executive Committee.

The American Heart Journal

VOL. 18

OCTOBER, 1939

No. 4

Original Communications

THE FORMATION AND MOVEMENTS OF LYMPH

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ALL who deal with the physiology of the body fluids encounter again and again the problem of the nature and composition of the extravascular environment. Four fluids must be considered as involved in the problem. They are (1) the blood plasma, (2) the capillary filtrate, (3) the tissue fluid, and (4) the lymph.

I believe that there is no longer serious debate as to the fact that typical normal blood capillaries, such as those in the skin and in the subcutaneous tissue, are somewhat permeable to serum albumin and serum globulin. These proteins are normal constituents of lymph wherever it is collected, and there can be no doubt that they filter from the blood capillaries practically all over the body. I pointed out, in 1933, that where capillaries are structurally specialized, as in the glomeruli and the choroid plexuses, the capillary membrane is in reality a two-layer affair, and does not resemble the typical capillary with its single layer of endothelial cells.

At the same time, capillaries have been held to vary greatly in permeability; this idea is based largely upon differences in the composition of lymph from different regions. For example, in Table I there are four estimations of protein in blood and in liver lymph. No other lymph in the body shows such high protein concentrations as these, but I am by no means sure that this is not a concentration phenomenon due to the extensive water requirements of the liver. We used to believe that a large fraction of the highly proteinized thoracic duct lymph came from the liver, but Markowitz and Mann¹ (1931), in experiments in which they were collecting thoracic duct lymph from dogs, found no diminution in the volume of this lymph after ligation of the periportal lymphatics, or even after removal of the liver. There

¹The George Brown Memorial Lecture, delivered at the Fifteenth Annual Meeting of the American Heart Association, St. Louis, Mo., May 13, 1930.

From the Laboratory of Physiology, Harvard School of Public Health.
Received for publication June 5, 1939.

is little doubt that in the quiescent, anesthetized animal at least 90 per cent of the thoracic duct lymph comes from the intestines. This lymph is rich in protein, and there has been much talk about the high degree of permeability of the intestinal capillaries. I am inclined to

TABLE I
PROTEIN CONCENTRATION IN BLOOD AND IN LIVER LYMPH FROM FOUR DOGS

DOG	TOTAL PROTEIN IN GRAMS PER CENT	
	BLOOD SERUM	LIVER LYMPH
1	7.64	6.20
2	6.16	4.45
3	5.91	5.56
4	5.66	5.10

think that this opinion rests on failure to realize the mechanical conditions which affect the circulation in the gut. Examine, for example, Mall's (1896) reconstruction of the blood vessels and lymphatics in the wall of the stomach, as seen in Fig. 1; considered mechanically, the same conditions recur through the entire intestinal tract. Observe that the arteries and veins supplying the very profuse network of blood capillaries must pass through heavy layers of muscle before ramifying as capillaries. I cannot present direct evidence as to pressures, but the arrangement clearly suggests the possibility that during peristaltic contractions venous pressure and, consequently, capillary pressure may rise. At the same time lymph will be squeezed toward the thoracic duct. The arrangement is beautifully adapted for the production and movement of lymph, so much so as to make one wonder whether the very profuse supply of intestinal capillaries consists of vessels which are specially permeable, or whether what has been interpreted as excessive permeability is not simply the expression of the physiologic setting in which the capillaries reside. So, in considering the permeability of capillaries, one can never think in terms of a simple membrane appropriately mounted for filtration in the chemical laboratory. It is necessary, first, to think of the histologic character of the membrane, whether it be reenforced, as in the glomeruli, or possibly latticed, as in the case of the spleen. Second, one must examine the setting of the capillaries, whether they are subjected, as in the gastrointestinal tract, to mechanical influences calculated to alter pressures in such a way as to produce filtration. Third, one must take into account a long list of chemical and physical conditions which have been held to affect filtration and attempt to decide whether they alter the membrane, or whether they alter pressure relations, and thereby induce greater filtration through an unchanged membrane. The most important of such conditions are the following:

1. Oxygen lack and carbon dioxide increase.
2. Activity of the tissue under observation.

3. Miscellaneous chemical and hormonal effects, such as the possible production of histamine, and such hormonal factors as those which influence the oestrus edema of the sexual skin in monkeys.

4. Increase and decrease of plasma protein concentration.
5. Temperature.
6. Capillary blood pressure.
7. Tissue pressure.
8. Contraction and dilatation of capillaries.
9. Arteriovenous anastomoses.

All of these factors, except the last, have large places in the literature of capillary permeability. The possible relation of arteriovenous anastomoses to capillary filtration is just beginning to be appreciated. These anastomoses were described in 1877 by Hoyer,² then forgotten, and now are moving into physiologic prominence after a period of extensive and profitable anatomization.

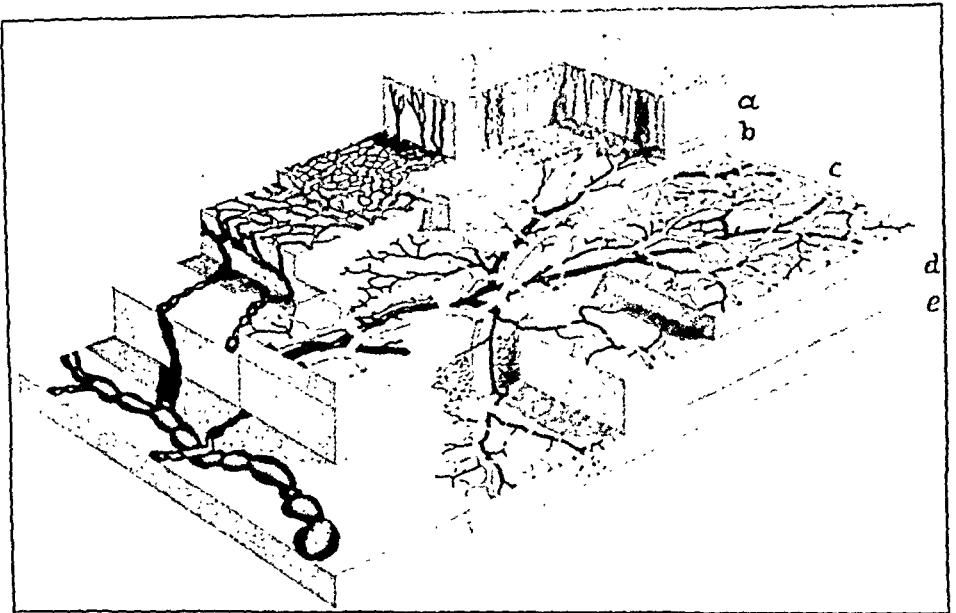


Fig. 1.—Reconstruction of a small portion of the middle zone of the stomach. The long diameter of the drawing is in the direction of the longitudinal muscle fibers. It was built up from 30 drawings, and each drawing is an exact representation of a specimen. Enlarged 20 times. *a*, mucous coat; *b*, muscularis mucosae; *c*, submucous coat; *d*, circular muscle; *e*, longitudinal muscle. (From Mall, F.: *The Vessels and Walls of the Dog's Stomach*, Johns Hopkins Hospital Reports 1: 1, 1896.)

They would seem to present a beautiful mechanism for preventing excessive capillary pressures when blood flow is extremely rapid. Let us consider an individual exercising violently. Capillary blood flow is enormously increased in order to provide the necessary oxygen, but excess pressure in the capillaries is in all probability prevented by opening of the arteriovenous by-passes. All of us who have perfused isolated organs have learned to use a by-pass of varying resistance in order to prevent excess pressures. In regard to filtration

from the capillaries, the arteriovenous anastomoses, when widely open, may thus be thought of as lessening the pressure head in the capillaries and increasing the load upon these vessels if they are contracted.

The admission that normal capillaries leak the blood proteins illustrates the usual plight of the physiologist. It simply pushes him on to another question: How permeable are the capillaries to protein, or, to put it in a more practical fashion, what is the nature of the capillary filtrate? Efforts to answer this question have been of two types. First, there have been attempts to cause increased capillary filtration, and then calculate the probable protein concentration of the filtrate. A noteworthy example of such experiments is that of Landis, Jonas, Angevine, and Erb³ (1932). They declared that the capillary filtrate in the human arm contained not more than 0.3 per cent of protein. Figures for the protein concentration of normal peripheral lymph are extremely few. Some years ago, White and I cannulated an ankle lymphatic in my associate, Miss Field. She walked about with the cannula in place, and the lymph produced contained 0.49 per cent of protein. This is a low figure, but it is certain that the fluid escaping from the blood capillaries is concentrated either where it passes out, or in a lymphatic trunk before it can be collected for analysis.

The second method of determining the nature of the capillary filtrate consists in the measurement of the protein content of edema fluid, particularly in cases of cardiac edema. Bramkamp⁴ (1935) provides a fairly recent example. In twenty-six patients with the edema of congestive heart failure, the protein varied from 0.03 to 0.54 per cent. In such persons reabsorption of water is considered not to occur, and the edema fluid is thus not only capillary filtrate but tissue fluid at the same time. It appears right to make this assertion for the conditions in question, but reabsorption of water is not prevented under normal conditions in healthy persons, and there is no valid reason to believe that concentration of extravascular fluid does not occur.

Again we are confronted by a question. If concentration of extravascular fluid occurs, are tissue fluid and lymph affected alike, or is concentration more prominent in one than in the other?

Actual collection of tissue fluid in the normal mammal has never been accomplished, but recently Maurer⁵ (1938) has succeeded in collecting tissue fluid from frog muscle. His method consisted in piercing the muscle longitudinally with a fine capillary tube. By an ingenious technique, he showed that because of the toughness of the sarcolemma the capillary invariably passed between muscle cells and did not wound them. When the tube was withdrawn it contained clear, straw-colored fluid, uncontaminated with blood. In nine samples of this tissue fluid Maurer found that the protein varied between 0.44 and 3.54 per cent,

with an average of 1.53 per cent. With Churchill and Nakazawa⁶ (1927), I found that the protein in the lymph of sixty frogs varied between 0.29 and 2.17 per cent, with an average of 1.0 per cent. The agreement is close enough to enable one to say that in the single instance in which tissue fluid has been obtained it is identical in composition with lymph. If such were found to be the case in the mammal, then lymph, which can be collected from many parts of the body and from isolated organs, such as the heart, would become an important instrument for physiologic analysis, in that it would really reflect the environment of the body cells.

But in the mammal the best direct evidence for the identity of tissue fluid and lymph is offered by studies in which, as edema develops, permitting the collection of tissue fluid, lymph has been obtained from the same part. Examples of such determinations are found in Tables II and III.

Several years ago we (Drinker, Field, and Homans,⁷ 1934) produced fairly complete obstruction of the lymphatics in the leg of the dog. Lymphedema develops slowly in such animals, and as it begins to appear a puncture wound will provide clear edema fluid. At the same time one may cannulate an ankle lymphatic and collect lymph. Table II presents data obtained in this way from four dogs. There is obviously close agreement between the values for protein concentration in the two fluids. Weech and his associates (1934)⁸ made precisely similar observations upon dogs rendered edematous by plasmapheresis, or by protein deprivation, which are listed in Table III. Again there is agreement in protein values.

Whether or not lymph and tissue fluid are reasonably identical in composition must continue to be the subject of experiment, and direct experiment if possible. But whatever the final result may be, there

TABLE II

SIMULTANEOUS PROTEIN VALUES IN LYMPH AND EDEMA FLUID FROM THE FEET OF DOGS RENDERED EDEMATOUS BY LYMPHATIC OBSTRUCTION

NO. OF ANIMAL	DATE	LYMPH PROTEIN (%)	EDEMA FLUID PROTEIN (%)
1	9/15/33	3.37	3.37
	4/ 3/34	2.48	3.45
2	4/ 9/34	2.55	1.86
3	2/25/33	2.67	2.00
	3/ 8/33	2.45	2.20
4	3/28/33	2.28	2.75
	5/ 5/33	2.97	3.17
	10/16/33	3.17	3.17
	4/ 6/34	2.50	2.67

can be no doubt that lymph is formed from the extravascular tissue fluid, and the state of this fluid in the tissues is thus a matter of consequence for us. All varieties of experiment show that in normal tissues

very little free fluid exists. A hypodermic needle thrust beneath the skin produces nothing. No one who has worked upon the physiology of lymph formation and movement in vessels other than the thoracic duct has ever failed to be annoyed by the small amounts of lymph obtained.

TABLE III

COMPARATIVE PROTEIN CONTENTS OF EDEMA FLUID AND THE LYMPH COLLECTED IMMEDIATELY AFTER CANNULIZATION

(From Weech, Goetsch, and Reeves⁸)

DOG NO.	HIND LEGS				FORE LEGS				ASCITIC FLUID	NATURE OF EDEMA
	RIGHT		LEFT		RIGHT		LEFT			
	EDEMA FLUID	LYMPH	EDEMA FLUID	LYMPH	EDEMA FLUID	LYMPH	EDEMA FLUID	LYMPH		
	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>	<i>cent per</i>	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>	
5	0.23	0.18								Nutritional
8-40	0.04		0.02	0.11					0.02	Nutritional
8-06	0.17	0.28	0.14	0.60		0.31		0.23	0.13	Nutritional
8-38	0.08	0.53		0.30		0.29			0.32	Nutritional
9-92						0.07		0.06	0.01	Plasmapheresis
6						0.32		0.15	0.03	Plasmapheresis
5-8	0.09	0.06	0.08							Plasmapheresis
9-1	0.86*	0.38	0.95*							Plasmapheresis
2-3			0.17	0.19	0.16	0.14				Nutritional
1-31	0.04	0.01	0.16*						0.01	Plasmapheresis

*These edema fluids contained blood.

Observations such as these have caused it to be held that the tissues contain no free fluid, that the extravascular environment is a sort of gel (Clark and Clark,⁹ 1933). While I am in absolute agreement with the conception that there is little free water in the tissues, I do not see how they can resemble a gel. One may thrust needles into gelatin as long as one pleases, and no water will escape, even though the gelatin is quite fluid. Also, if there is no free fluid in the tissues, how does one account for the fact that though lymph is ordinarily small in amount, still it is there, and no one has ever demonstrated glandular activity for lymphatic endothelium, secretory ability such as is possessed by the salivary glands in abstracting water and other substances from the blood. The formation and composition of lymph depend on the status of the tissue at the moment. Thus, Field and Drinker¹⁰ (1931) found that the protein content fell and the rate of lymph flow rose promptly when dogs were subjected to acute plasmapheresis, and Haynes¹¹ (1932) showed that immediately after severe hemorrhage lymph flow fell and lymph protein became more concentrated.

As far as I can see, all evidence indicates that the lymph keeps closely in touch with the extravascular environment, and the prime function of the lymphatics is to remove extravascular protein which in their absence accumulates and leads to edema. The lymphatic endo-

thelium is apparently very permeable to the blood proteins and to many things of even larger size which do not enter the blood when deposited in the tissues.

The formation of lymph is thus, first of all, dependent upon the amount of free fluid in the tissues, and, second, upon influences which empty draining lymphatics and permit further absorption of raw material by lymphatic capillaries. Let me illustrate by picturing the situation in the skin and subcutaneous tissues when edema occurs. If histamine is injected into the skin, edema occurs rapidly and the free fluid in the tissue is at once increased. In the loose connective tissue one sees separation of fibers, and on careful observation it soon becomes apparent that the lymphatics are becoming dilated. Pullinger and Florey¹² (1935), whose work is shown in Fig. 2, found that lymphatic capillaries are attached to surrounding tissues. When edema occurs, though tissue pressure may be increased, they are pulled open, and the permeability of their walls for the constituents of the edema fluid causes them to fill with it. If edema formation is abrupt and continuous, the mere fact of its existence may produce lymph flow from trunks draining the part. Some years ago we cannulated an ankle lymphatic in a dog and then dipped the foot in very hot water for two minutes. The foot swelled rapidly, and lymph which was practically blood plasma flowed in a steady stream from the cannula, which was placed well above the lesion. But to secure an increase in lymph flow from edema alone one needs a rapid, marked increase in tissue pressure, and in the ordinary congestive edema this does not occur. If, however, the edematous part is massaged or moved actively or passively, lymph flow will be more rapid than normal. The bedridden patient with cardiac edema delivers exceedingly little edema fluid back to the circulation via the lymphatic system. Only by movement or massage can any impression be made.

Too much of our information upon the normal movements of lymph has been based on data concerning the flow from the thoracic duct in quiescent, anesthetized animals. Under such circumstances practically all of the lymph collected comes from the gastrointestinal tract and from the heart. It is usually thought that one obtains very little thoracic duct lymph unless the animal is digesting fat. This is not so. The thoracic duct lymph owes its volume to the intestinal blood capillaries which supply the water and the protein of the lymph. The actual volume of fat absorbed is small; in fact, one often gets the largest volumes of thoracic duct lymph after fat deprivation. A good circulation and active peristalsis are the factors which cause free movement of lymph from the intestine.

Of greater interest to us are the ordinary movements of lymph in such regions as the skin. The extent of the lymphatic capillary system

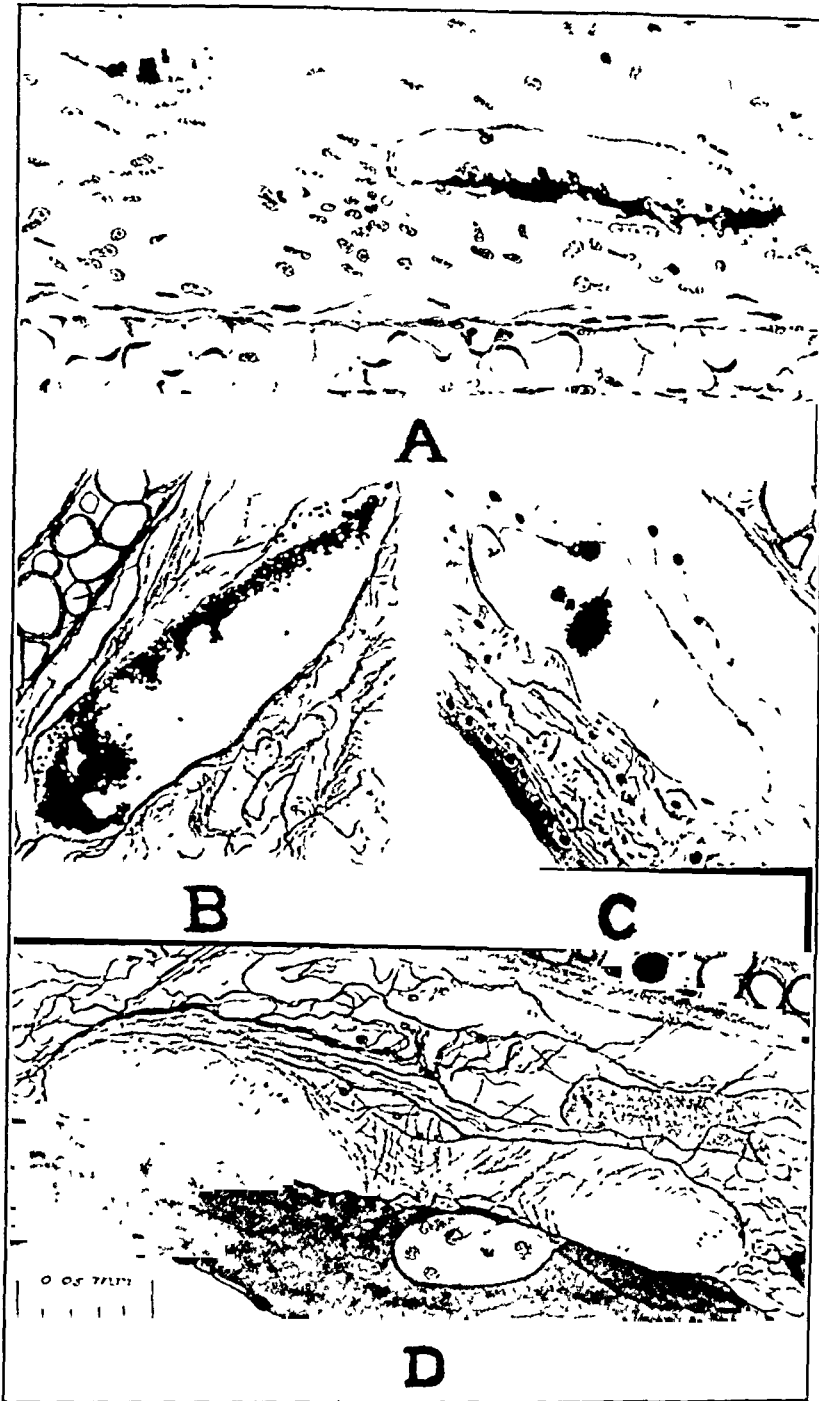


Fig. 2.—4. Histamine edema in mouse's ear. Widely opened lymphatics containing hydrokollag, superficial to skeletal muscle bundles. Connective tissue fibers attached to walls. Stained with iron-hematoxylin and van Gieson. B. Histamine edema in mouse's ear. Deep lymphatic near central cartilage, widely open, containing hydrokollag and with connective-tissue fibers attached to walls. Silver impregnation. C. Histamine edema in mouse's ear. Superficial lymphatic containing hydrokollag, widely dilated. Wall attached to collagen fibers in the corium. Stained with azan. D. Superficial lymphatic in edematous ear in a section 14μ thick, showing wall, cut tangentially, composed of interlacing fibers of collagen and reticulum. Silver impregnation. The dark mass at the bottom is skin epithelium. (From Pullinger and Florey¹².)

in the skin is little appreciated. Fig. 3 is a reconstruction of the capillary lymphatics of the skin. There are two plexuses, a superficial one just beneath the epithelium, containing few valves, and a second in the deeper part of the corium and in the subcutaneous areolar tissue beneath it. The two plexuses communicate freely and empty into large valved trunks which are found close to the veins. The arrangement is, in effect, an enormous superficial net containing very few valves in the outer part, and continuous all over the body. In the outer plexus lymph will move in any direction decreed by gravity, by motion, or by massage. The difficulty of obstructing the superficial network is obvious enough. Nothing short of complete destruction will accomplish it. The anatomic arrangement makes it

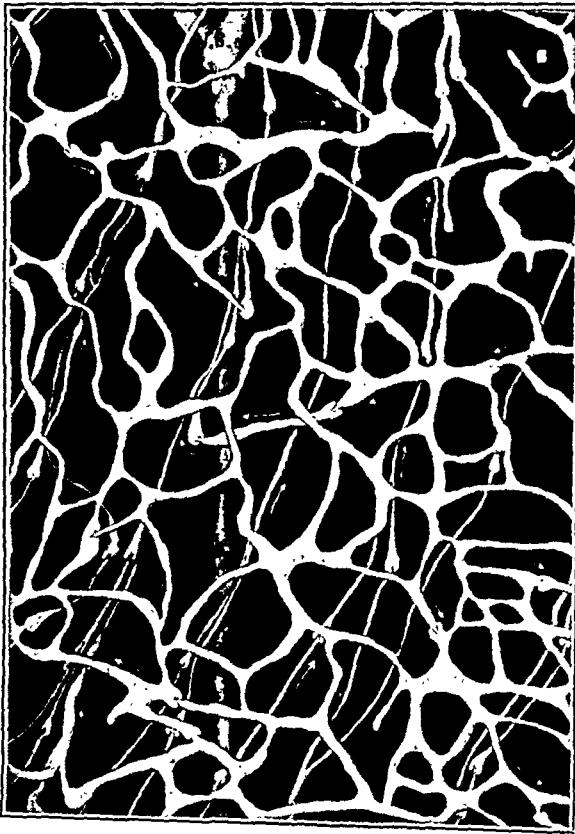


Fig. 3.—Reconstruction of a small portion of the lymphatic plexus in the cutaneous and subcutaneous area of the leg of a 130-mm. (4.3 months) fetus. $\times 66\%$. White rectangle in the upper corner indicates natural size of the area shown. Note the numerous valves, and the drainage of the subcutaneous plexus into the deeper, more regularly disposed, and more slender lymph channels. *v.s.*, vena saphena magna. (From Kampmeier, O. F.: *The Genetic History of the Valves in the Lymphatic System of Man*, *Am. J. Anat.* 40: 413, 1928.)

clear that if one gets obstruction of the deeper lymphatics in a part, it is still sometimes possible to discover superficial vessels; and if the part is massaged or given opportunity to drain by gravity, lymph may find its way in the meshwork as the external force directs it.

Recent work (Forbes,¹³ 1938) indicates that there is free communication between skin lymphatics across the midline of the body and gives no indication that local areas are separated from other parts, as has often been thought.

It is easy to collect skin lymph from a cannulated ankle lymphatic in a dog. In Fig. 4 the position of the cannula is shown. It is inserted under local anesthesia, and then the dog may walk or run quite normally for many hours. When he lies quietly no lymph flows from the cannula. When he walks at a uniform rate lymph flow soon becomes quite steady. I¹⁴ described different facts learned by means of this preparation in a Harvey Lecture last year and will not review the material again, but I do wish to point out one thing. If we cause such an animal to walk until lymph flow becomes constant, and then permit him to rest for half an hour before again walking at the same rate, he will invariably begin the new period of movement with a large flow of lymph which will decrease as walking continues. When he lies still no lymph leaves the part, and fluid apparently accumulates until tissue pressure balances filtration pressure. Under these circumstances water and crystalloids may be absorbed by the blood capillaries and replaced from them, but, after a time, loss of protein from the capillaries must be slight. As soon as the animal walks, tissue fluid and lymph are caused to enter and move in the lymphatics, and capillary filtration may again become active.

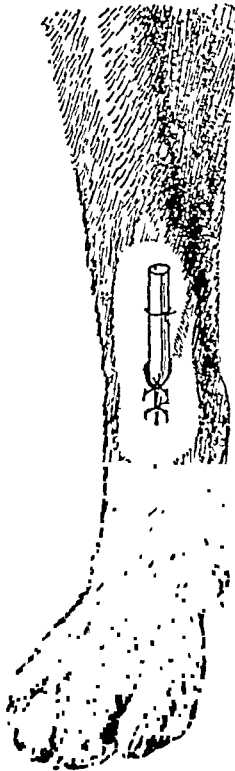


Fig. 4.—Front leg of dog with cannula in a collecting lymphatic and tied to the skin. (From Drinker, C. K., and Field, M. E.: *Lymphatics, Lymph and Tissue Fluid*, Baltimore, 1933, p. 89, Williams and Wilkins Company.)

During the past winter we have made a new preparation which permits us to obtain lymph in a normal manner from anesthetized animals

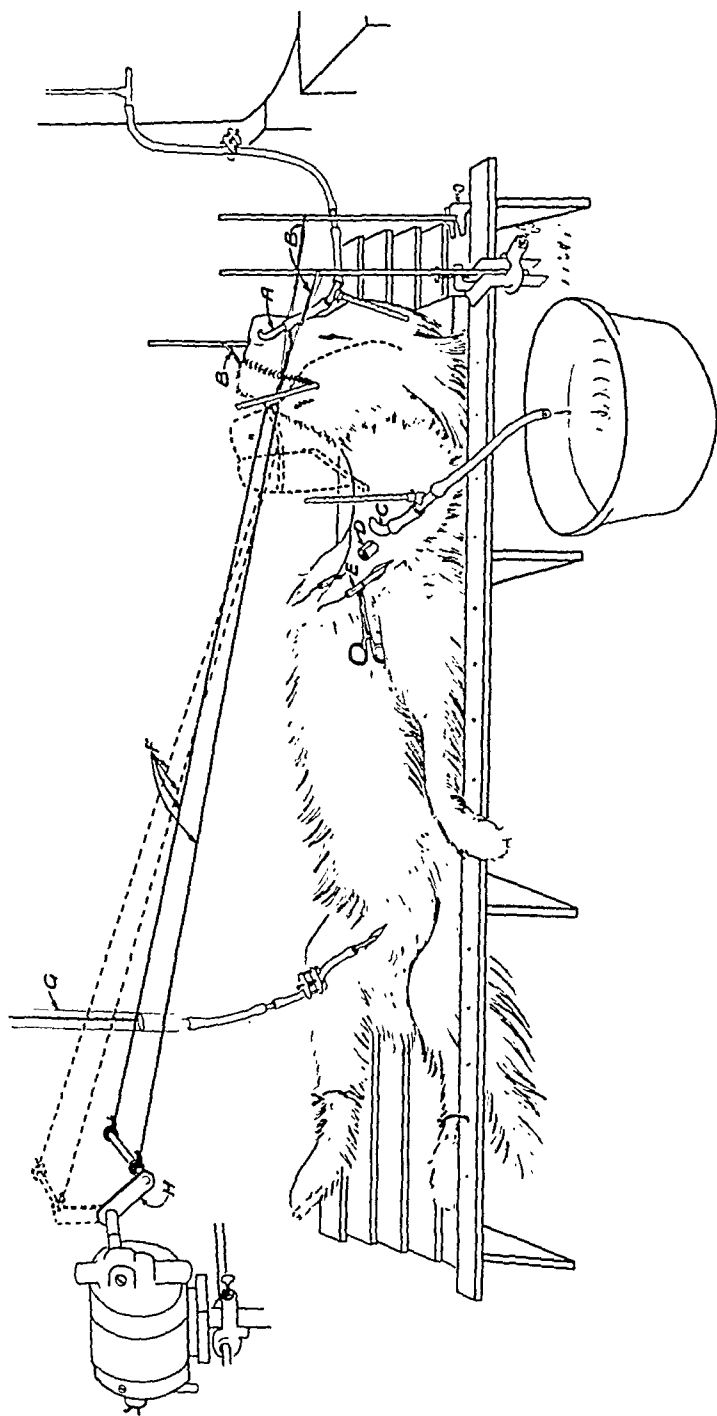


Fig. 5.—Diagram of apparatus for passive motion of the head and perfusion of the nasopharynx. *A*, inflow perfusion tube from constant temperature reservoir to nostril; *B*, rubber bands; *C*, outflow perfusion tube tied into trachea; *D*, tracheal cannula; *E*, cannulae in cervical lymphatics; *F*, twine attaching snout to crank; *G*, burette attached to cannula in femoral vein; *H*, electrical-ly driven crank. When the motor rotates the crank, *H*, the head is flexed, and the rubber bands, *B*, return it to the usual prone position. This slight passive motion results in a constant flow of cervical lymph and produces ideal conditions for studying the absorption of various substances from the nasopharynx. (From McCarrell¹⁵.)

(McCarrell,¹⁵ 1939). Lymph in this case is obtained by cannulating both cervical lymphatic trunks at about the middle of the neck. By exclusion, we have determined that most of the lymph obtained comes

from the nasopharyngeal mucosa. We have used the preparation to study lymphatic absorption from the surface of the nasopharynx, but it applies to much besides. After the lymphatics have been cannulated, a cannula (*D*, Fig. 5) is placed in the trachea, and an L tube (*C*, Fig. 5) is inserted in the trachea above it. The snout of the dog is now attached to a rotating bar, and by elastic bands to uprights upon the animal board. Under anesthesia and quiescence one obtains little or no cervical lymph from the dog; but if the rotator operates, the head nods deliberately ten times a minute and lymph flows steadily from the cannulated vessels as long as one cares to make observations. Many things may be accomplished. For example, suppose a catheter is inserted in the nose. Physiologic salt solution, at any temperature, with any sort of addition one pleases, may be irrigated through the nasopharynx and out of the L tube in the trachea. In Fig. 6 is displayed the type of information which may be elicited. The upper curve gives the protein concentration of the lymph in per cent, the middle curve the volume of lymph per minute in milligrams, and the lower curve the lymph protein in milligrams per minute. After a period of about forty-five minutes,

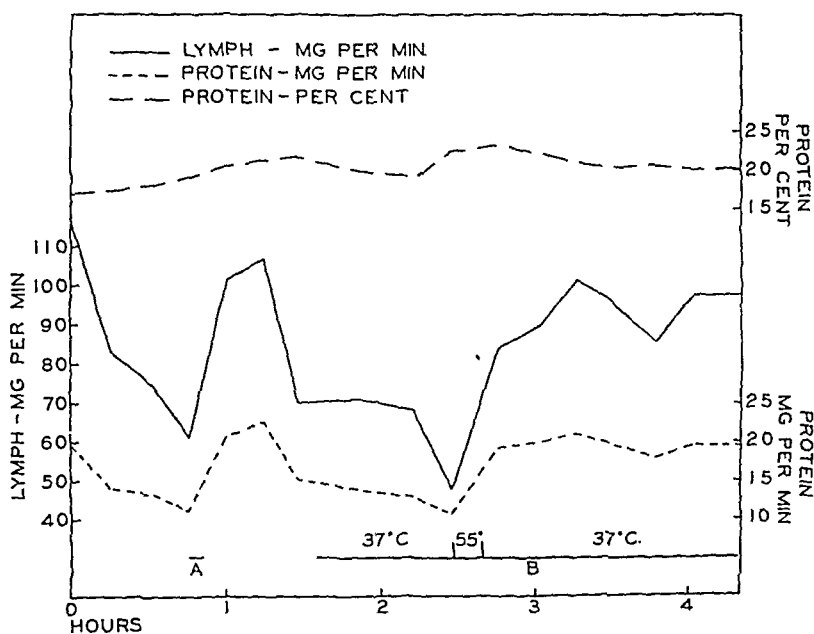


Fig. 6.—Chart illustrating sensitivity of method. The upper curve shows the percentage of protein in the pooled lymph from both cervical ducts of a dog. In the lower curves are charted the total amounts of lymph and of lymph protein collected per minute. During A, the external jugular veins were clamped for six minutes; during B, the nasopharynx was perfused with Ringer's solution at the temperatures indicated. Note the changes in cervical lymph flow and in protein content caused by the increase in venous pressure and by the local application of heat (55° C.). (From McCarrell¹⁵.)

during which lymph flow falls, as is always the case when activity succeeds quiescence, the two external jugular veins were clamped in order to produce an increase in capillary pressure. Observe the immediate effect upon the volume of lymph and upon the amount of protein collected. The nasopharynx was then irrigated with Ringer's solution at

37° C. This had no effect, even though the irrigation was continued for almost an hour. But when the temperature of the irrigating solution was increased to 55° C., there was an immediate and permanent increase in lymph production. This expresses capillary injury. Water at 55° C. can be taken in the mouth, but it is at the very limit of endurance, and there is no doubt that under the circumstances of the experiment the capillaries have been damaged.

If heat is applied, gradually increasing lymph formation begins at about 42° C., and changes not readily reversible begin to appear around 50° C. The lesson of such experiments is simple enough. One can expect decided increases in tissue fluid with tissue temperatures around 42 to 45° C., just about the limit of one's tolerance for heat. If it is of advantage therapeutically to increase both the vascular and extravascular circulation, then it is obvious that a part should be heated and at the same time massaged mechanically or moved passively.

As physicians interested in the circulation I believe you will be interested in a final phase of the problem. In studies upon lymph it is always difficult to obtain material which comes from a single tissue. Recently we have been able to do this in the case of the heart. It is a fortunate circumstance for the physiologist that the lymphatic drainage of the heart concentrates between the superior vena cava and the innominate artery, where cannulation may be accomplished. The result gives part of the lymph coming from the heart. Table IV shows that the rate of lymph flow and the composition of the lymph are closely related to the degree of cardiac activity, and I believe that through heart lymph we may possess a new instrument for uncovering the physiology of the heart, both in health and in disease.

TABLE IV
CARDIAC LYMPH

TIME P.M.	AMOUNT OF LYMPH	PROTEIN	
	MG. PER MIN.	MG. PER MIN.	PER CENT
12:25	6.61	2.10	3.33
12:40	18.70	5.10	2.73
12:55	30.09	7.82	2.60
1:10	21.51	5.59	2.60
1:25	18.13	4.68	2.58
1:40	16.64	4.44	2.67
1:55	16.12	4.43	2.75
2:10	16.73	4.53	2.71
2:55	14.60		
3:10	20.49		
Average	18.36	4.84	2.75
3:10-3:20	Adrenin injected into jugular vein		
3:25	63.40	17.43	2.75
3:40	57.94	17.38	3.00

In conclusion, let me point out that I have been describing direct experiments on a part of the circulation which has been too much neglected, or has been the subject of calculations and deductions through indirect methods. It is a system acknowledged to play a potent part in disease, but few clinicians have knowledge even of its anatomic extent. I have been much honored in being permitted to call your attention to the possibilities of thinking in terms of the lymphatics, and hope that my introduction may lead to offspring in the shape of contributions to the clinical physiology of the lymphatic apparatus, in addition to your regular productions upon the circulation of the blood.

REFERENCES

1. Markowitz, C., and Mann, F. C.: Studies on the Physiology of the Liver. XXI. The Role of the Liver in the Formation of Lymph, *Am. J. Physiol.* 96: 709, 1931.
2. Hoyer, H.: Ueber unmittelbare Einmündung kleinster Arterien in Gefäßäste venösen Charakters, *Arch. mikr. Anat.* 13: 603, 1877.
3. Landis, E. M., Jonas, L., Angevine, M., and Erb, W.: The Passage of Fluid and Protein Through the Human Capillary Wall During Venous Congestion, *J. Clin. Investigation* 11: 717, 1932.
4. Bramkamp, R. G.: The Protein Content of Subcutaneous Edema Fluid in Heart Disease, *J. Clin. Investigation* 14: 34, 1935.
5. Maurer, F. W.: Isolation and Analysis of Extracellular Muscle Fluid from the Frog, *Am. J. Physiol.* 124: 546, 1938.
6. Churchill, E. D., Nakazawa, F., and Drinker, C. K.: The Circulation of Body Fluids in the Frog, *J. Physiol.* 63: 304, 1927.
7. Drinker, C. K., Field, M. E., and Homans, J.: The Experimental Production of Edema and Elephantiasis as a Result of Lymphatic Obstruction, *Am. J. Physiol.* 108: 509, 1934.
8. Weech, A. A., Goettsch, E., and Reeves, E. B.: The Flow and Composition of Lymph in Relation to the Formation of Edema, *J. Exper. Med.* 60: 63, 1934.
9. Clark, E. R., and Clark, E. L.: Further Observations on Living Lymphatic Vessels in the Transparent Chamber in the Rabbit's Ear—Their Relation to the Tissue Spaces, *Am. J. Anat.* 52: 273, 1933.
10. Field, M. E., and Drinker, C. K.: The Rapidity of Interchanges Between the Blood and Lymph in the Dog, *Am. J. Physiol.* 98: 378, 1931.
11. Haynes, F. W.: Factors Which Influence the Flow and Protein Content of Subcutaneous Lymph in the Dog. I. Hemorrhage and Hyperemia, *Am. J. Physiol.* 101: 223, 1932.
12. Pullinger, B. D., and Florey, H. W.: Some Observations on the Structure and Functions of Lymphatics: Their Behaviour in Local Oedema, *Brit. J. Exper. Path.* 16: 49, 1935.
13. Forbes, G.: Lymphatics of the Skin, With a Note on Lymphatic Watershed Areas, *J. Anat.* 72: 399, 1938.
14. Drinker, C. K.: The Functional Significance of the Lymphatic System, *Bull. New York Acad. Med.* 14 (series 2): 231, 1938; *The Harvey Lectures, Series XXXIII, 1937-1938*, p. 89.
15. McCarrell, J. D.: Lymphatic Absorption from the Nasopharynx, *Am. J. Physiol.* 126: 20, 1939.

THE CORONARY ARTERIES OF THE DOG

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BEFORE experimenting on the coronary circulation it is necessary to become familiar with its anatomic peculiarities. With this purpose in mind, I performed numerous dissections in the dog and found certain things which were not in agreement with previous descriptions of the coronary arteries in this species. Since the dog is much used at this time for experiments of this nature, I thought it might be worth while to publish my observations, with a concise but complete description of the anatomy of the coronary arteries of the dog.

TECHNIQUE

The heart was removed immediately after death; its cavities were washed out with tap water; and it was placed in the refrigerator, at 5° to 10° C., for twenty-four hours. The main trunks of the coronary arteries were then dissected, and threads were placed on them for tying the cannulas used for injection. These were placed after the aorta, free from the pulmonary artery and surrounding tissue, had been opened by dividing it lengthwise down to its origin. The coronary system was washed out with warm (45° C.) saline, and then a radiopaque colored mixture was injected. The method of injection and the lead acetate, sodium diphosphate, and agar mixture were those recommended by Schlesinger.¹

Roentgenograms were made of the anterior and lateral aspects of the heart; the viscus was then opened by Schlesinger's method of section and more roentgenograms made. A dissection of the minor branches, using the roentgenograms as guides, was then carried out.

For purposes of description the heart is considered as having an anterior and a posterior aspect, a left border (*margo obtusus*) and a right border (*margo acutus*), a base and an apex. The aortic cusps will be named according to their position: anterior right, anterior left, and posterior.

Altogether, thirty-one hearts have been studied, although some were only partially injected. They were obtained from dogs differing greatly in size, weight, age, and breed. For this reason, measurements are valid only for the individual observed and are given only for illustration.

DESCRIPTION

Authors describe two coronary arteries in the dog, the left and the right. Moore² found two right coronary arteries in 20 per cent of his animals. I have found constantly two left coronary arteries, the circumflex and the anterior descendens (*a. sulci longitudinalis anterioris*); in nearly one-third of the cases the septal artery also had an independent origin, and, more rarely, a fourth artery, which runs diagonally down the anterior aspect of the left ventricle, may be found. Usually only one right coronary artery was seen, but in some dogs there were two, and even three.

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Received for publication March 10, 1939.

Left Circumflex Coronary Artery.—This originates in a small fossa, or depression, in the aortic wall, situated, in 79 per cent of the animals, on a level with the edge of the anterior half of the anterior left aortic cusp, somewhat further back in the remaining 21 per cent. The diameter of the depression varies with the size of the dog, being about 4 mm. in a 20 kg. animal; its depth corresponds to the thickness of the aortic wall. The anterior descendens also originates in this fossa, to the right of the circumflex, but there is no common trunk as there is in man.

The circumflex artery runs in the left auriculoventricular sulcus; its first part is covered by the left auricular appendix; on reaching the sulcus longitudinalis posterior it descends along it toward the apex (*r. sulci longitudinalis posterioris*). In no case did the circumflex end before reaching the posterior longitudinal groove; this corresponds to Banghi and Crainicianu's type IV in man.

The length of the artery varies from 55 to 160 mm., depending on the size of the animal; its diameter near the aortic orifice varies from 1 to 2.5 mm.

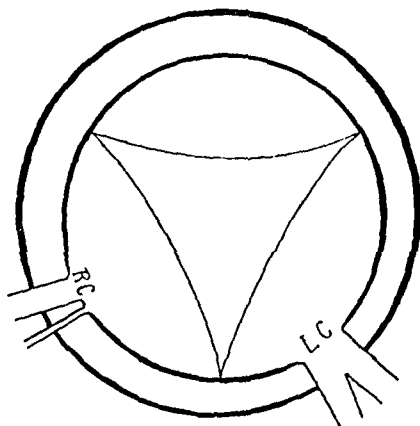


Fig. 1.—Origin of the coronary arteries in the aorta.

The *branches* of the circumflex can be distinguished as descending, or ventricular, and ascending, or auricular. There are two to six principal *ventricular branches*, and several minor ones. The most prominent are: (1) a branch leaving the circumflex at the level of the left border and descending toward the apex, usually ending 10 to 15 mm. before reaching it (*r. marginis obtusi*); (2) a branch arising shortly before the circumflex starts to descend, going to the posterior aspect of the right ventricle (*r. ventriculi dextri posterioris*); and (3) the terminal branch (*r. descendens posterior aut sulci longitudinalis posterioris*), which ends at the apex, or shortly before. Its length varies, depending on the size of the dog, from 25 to 85 mm.; it gives out branches to the posterior aspect of the left ventricle and the left papillary muscles. Shorter branches supply a narrow strip, about 10 mm. wide, of that part of the right ventricle contiguous to the posterior longitudinal groove, and several small branches penetrate the septum; but I have not

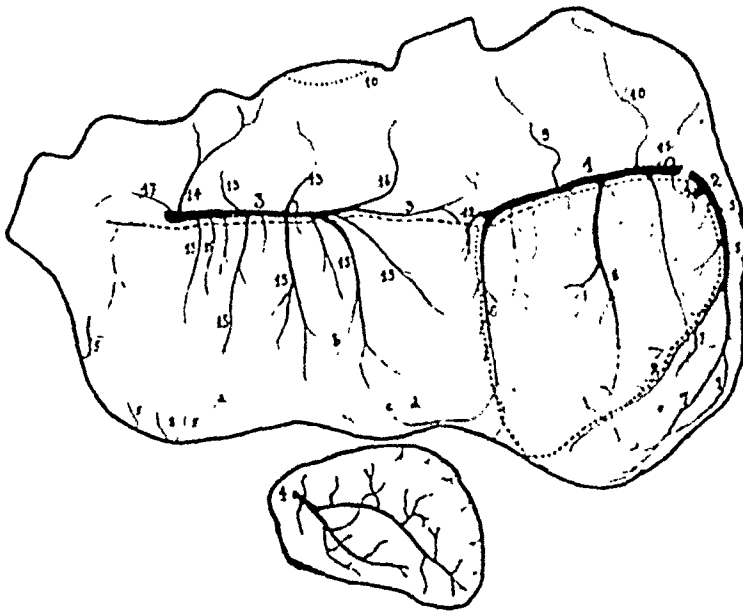


Fig. 2.—The coronary system of the dog: 1, circumflex artery; 2, a. descendens anterior; 3, right coronary artery; 4, a. septum ventriculorum; 5, r. ventriculi dextri; 6, r. sulci longitudinalis posterioris; 7, r. ventriculi sinistri; 8, r. marginis obtusi; 9, 10, and 11, r. atrialis sinister; 12, r. ventriculi dextri posterioris; 13 and 14, r. atrialis dexter; 15, r. ventriculi dextri; 16, r. atrialis dexter posterior; 17, r. adiposa; a, b, c, d, e, anastomoses.

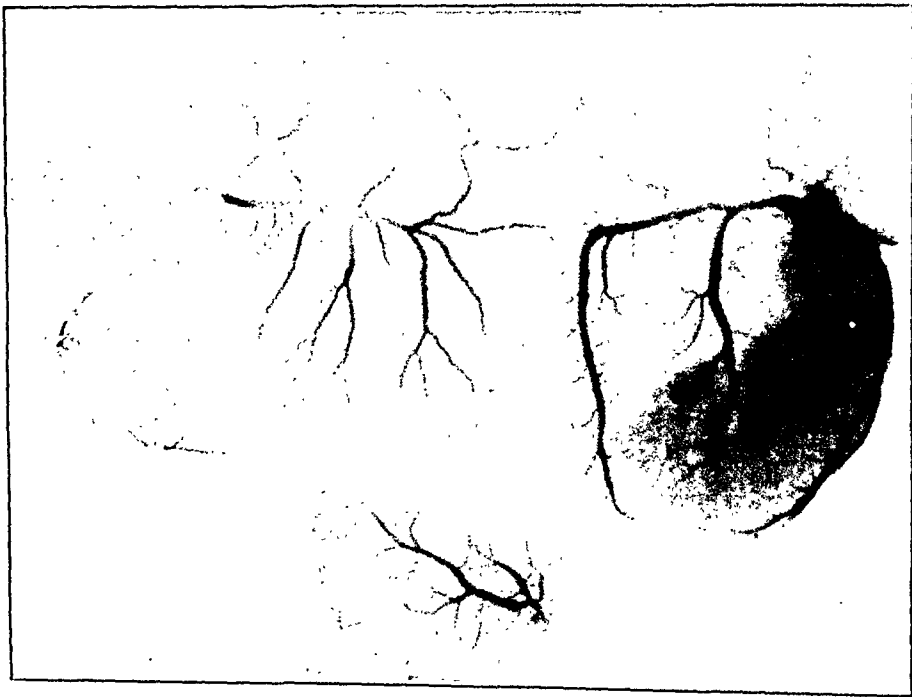


Fig. 3.—The coronary system of the dog's heart injected, spread out, and radiographed according to Schlesinger's method.

found one which could be individualized as was that described by Bianchi and Spalteholtz (quoted by Condorelli³), irrigating, in some cases, the fibrous part of the septum. According to Haas and Kalm (quoted by Condorelli), this small artery nourishes the auriculoventricular node and the bundle of His, the branches of the bundle being supplied by the septal artery. Owing to its inconstancy, all of the auriculoventricular conduction system can receive its blood supply from the septal artery.

The ascending, or *auricular branches*, are two to four in number. Near the origin of the circumflex a branch is sent to the left auricular appendix, in some cases. In others it is given off by another branch of the circumflex, the *r. atrialis sinister anterior*. This nourishes the anterior and superior aspects of the left auricle, and, in 75 per cent of my cases, contributed to the supply of the sinoauricular node. In my series this branch never originated from the *a. descendens anterior*, as was noted by Condorelli. Other branches of the circumflex go to the posterior aspect of the auricle and the interauricular septum.

Anterior Descending Coronary Artery (a. descendens anterior, a. sulci longitudinalis anterioris).—This originates in the left coronary fossa to the right of the circumflex artery; it runs down the anterior longitudinal sulcus, ending, in some cases, a little (not more than 20 mm.) above the apex; in others it not only reaches the apex, but also goes up the posterior aspect a short way. Its length varies, depending on the size of the dog, from 60 to 110 mm., and its diameter near its origin varies from 1 to 2.5 mm.

The branches of this artery supply the anterior aspects of the left and right ventricles and the septum. The branches to the left ventricle are three to seven in number. One arises about 40 mm. from the origin of the artery; it is constantly found, and, because of its size, v. Schulthess-Rechberg (quoted by Condorelli) has named the site of its origin the "division of the anterior descending branch." In four of my thirty-one animals the first branch arose directly from the aorta in the left coronary fossa already described. It runs diagonally down the anterior aspect of the left ventricle, giving off small branches; it should be called *ramus ventriculi sinistri primus*, or, when originating in the aorta, *arteria ventriculi sinistri prima aut diagonalis*. Moore² describes this branch as originating from the circumflex.

The branches to the right ventricle number three to five; with the exception of the first one, they are all very small; they supply a narrow band, not more than 15 mm. wide, of the anterior aspect of the right ventricle, adjacent to the sulcus longitudinalis anterior.

The branches going to the septum are very small and short with the exception of the first one. This last originated, in 70 per cent of my animals, about 5 mm. from the source of the anterior descending artery, but in the other 30 per cent it arose directly from the left coronary

fossa. I have never seen it originate from the circumflex, as Baumgarten (quoted by Condorelli) has. Because of its constancy, importance, and not infrequently independent origin, it should be called *arteria septum ventriculorum*. This septal branch, or artery, penetrates the septum at its anterosuperior angle and ends in the posteroinferior angle. At first it lies superficially with respect to the right ventricular cavity, covered by only a few muscular strands. The second half penetrates deeply into the septum; it has numerous branches, of which the first, going upward, and the second, running downward, can always be individualized. This artery supplies the right papillary muscles and the whole septum, with the exception of the anteroinferior angle, which is nourished by the anterior descending artery, and the posterior border, which is irrigated by the terminal branch of the circumflex.

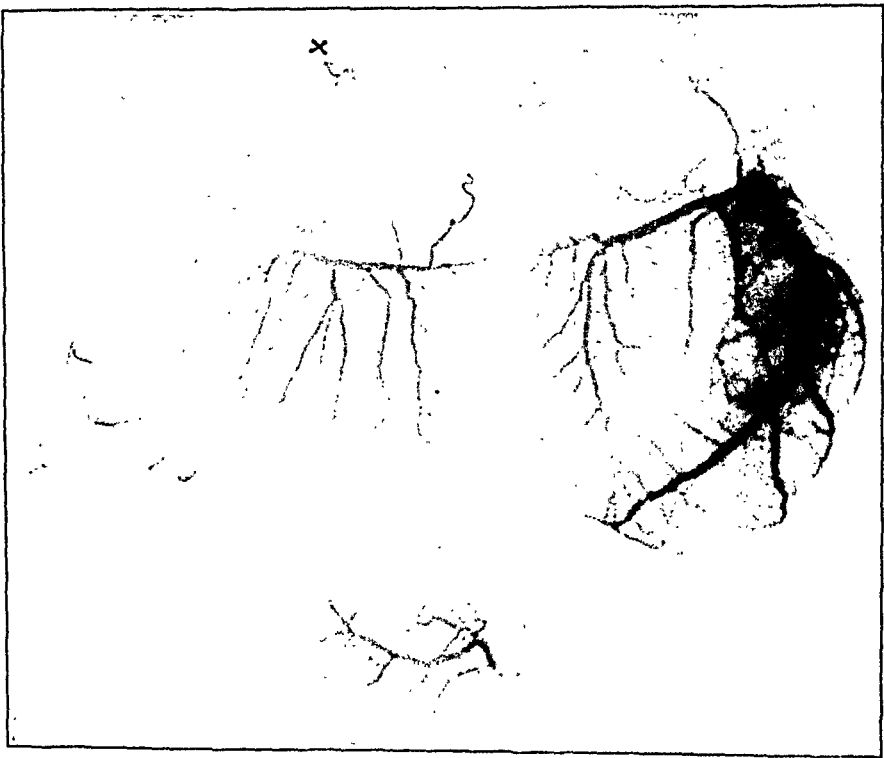


Fig. 4.—Coronary system of the dog: x, branch of the ramus atrialis sinister anterior irrigating the sinoauricular region (16 in Fig. 2).

Right Coronary Artery.—This artery arises at the middle of the anterior right aortic cusp. In 40 per cent of my dogs there were two right coronary arteries, a principal and an accessory one. The latter, when it exists, is small and short; it usually originates in a small orifice at the anterior edge of the principal artery; less frequently it originates about 1 mm. in front of this ostium; it runs in a forward and downward direction, supplying a small portion of right ventricle below the origin of the pulmonary artery.

The principal right coronary artery lies in the right auriculoventricular groove in the midst of abundant fatty tissue; its first part is covered by the right auricular appendix. Ellemberger and Baum⁴ and Condorelli³ maintain that the right coronary artery does not pass the margo acutus in the dog; Ellemberger and Baum describe a *r. marginis acuti* as the terminal branch. Bianchi (quoted by Condorelli) also agrees that the right coronary supplies only the anterior and lateral aspects of the right ventricle. In my animals this artery always invaded the posterior aspect, ending about 5 mm. from the sulcus longitudinalis posterior. Its length varied between 30 and 65 mm., and its diameter between 1 and 1.5 mm.

The branches can be divided into descending, or ventricular, and ascending, or auricular. The ventricular branches number four to nine; none is especially remarkable for its size or constancy, and there is not even a constant *r. marginis acuti*; they supply the walls of the right ventricle, but nowhere do they reach its borders, which are nourished by other arteries.



Fig. 5.

Fig. 6.

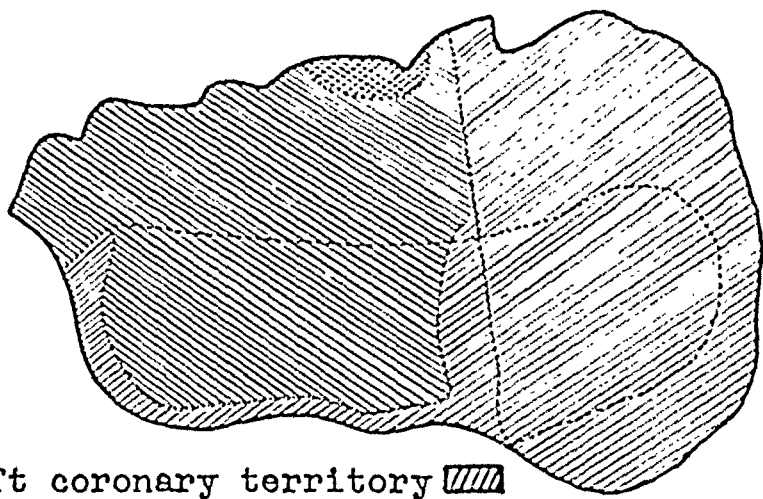
Fig. 5.—Anterior aspect of the heart injected and radiographed.


Fig. 6.—Left aspect of the heart, injected and radiographed.


The auricular branches are three to five in number; they supply the right auricle. The first branch goes to the right auricular appendix. The most important is the *r. atrialis dexter posterior*, which irrigates the walls of the right auricle, the interauricular septum, and the sinoauricular node. This distribution coincides with that found by Maldo-

nado-Allende and Orías,⁵ but differs from that described by Condorelli, who maintains that the S-A node is supplied by the *r. atrialis dexter anterior*. In this series the most important atrial branch of the right coronary artery originated near the end of the artery on the posterior aspect of the auricle, after the origin of an anterior branch and one or more of smaller caliber that could be denominated intermediate branches. It is, therefore, called *r. atrialis dexter posterior*, rather than *intermedius*, as it was designated by Meek, Keenan, and Theisen.⁶ The territory irrigated by Meek, Keenan, and Theisen's *r. intermedius* is about the same as that supplied by the *r. posterior*, but the origin described is more proximal than that found in this series.

I have not been able to demonstrate the *a. adiposac* which Bianchi (loc. cit.) has found in all cases. As they arise very near the origin of the main arteries, I suppose they were not injected by the method I employed.



Left coronary territory 

Right coronary territory 


A-V node region 

Fig. 7.—Left coronary territory, right coronary territory, and A-V node region supplied by right and left coronary arteries.

Anastomoses.—The existence of anastomoses can be shown when performing the saline injection; the fluid injected through a cannula placed in one artery flows out of the other arteries. Following Schlesinger's technique it is possible to locate these anastomoses by dissection. I have found fine connections between the ventricular branches of the right coronary artery and the right ventricular branches of the anterior descending artery and the terminal branches of the circumflex (*r. descendens posterior*). Also, I have seen anastomoses between the *r. marginis obtusi* and the left ventricular branches of the anterior descending artery. Communication is thus established between the territories of the three principal coronary arteries (right coronary, anterior descending, and circumflex). This by no means pretends to be a com-

plete list of all the anastomoses that exist; Baumgarten and Spalteholz (quoted by Condorelli) maintain that they are very numerous.

Areas of Blood Supply.—As in other animals, but differing from man, in the dog the left coronary arteries supply a larger territory than the right coronary artery. The latter nourishes only the right auricle, the interauricular septum, and the middle parts of the right ventricle. The circumflex coronary artery supplies the left auricle, the lateral and posterior aspects of the left ventricle, the posterior edge of the interventricular septum, and a narrow strip of the posterior aspect of the right ventricle. The anterior descending coronary artery supplies the anterior aspect of the left ventricle, that part of the anterior aspect of the right ventricle adjacent to the anterior longitudinal groove and the apex, and the interventricular septum. The sinoauricular node receives its blood supply from the right coronary artery and (75 per cent of my observations) also from the *r. atrialis anterior* of the circumflex.

I wish to thank Professor J. T. Lewis for the help and encouragement he has given me in the preparation of this paper.

REFERENCES

1. Schlesinger, M. J.: An Injection Plus Dissection Study of Coronary Artery Occlusions and Anastomoses, *AM. HEART J.* 15: 528, 1938.
2. Moore, R. A.: The Coronary Arteries of the Dog, *AM. HEART J.* 5: 743, 1930.
3. Condorelli, L.: Die Ernährung des Herzens und die Folgen ihrer Störung, Dresden und Leipzig, 1932, Steinkopff.
4. Ellemberger, W., et Baum, H.: Anatomie descriptive et topographique du chien (Transl. by J. Deniker). Paris, 1894, C. Reinwald et Cie.
5. Maldonado-Allende, I., and Orías, O.: Perturbaciones hemodinámicas consecutivas a la oclusión de la coronaria derecha en el perro, *Rev. Soc. Argent. Biol.* 12: 279, 1936.
6. Meek, W. J., Keenan, M., and Theisen, H. J.: Auricular Blood Supply in the Dog; General Auricular Supply With Special Reference to Sinoauricular Node, *AM. HEART J.* 4: 591, 1929.

HYPERTONIC GLUCOSE SOLUTION IN ANGINA PECTORIS

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SINCE glucose is a fundamental nutritive substance for all tissues and organs of the body, it has found very extensive use in medicine. Recently several investigators observed that the isolated heart, when perfused with glucose, responded with stronger contractions. Hence, its clinical use seemed logical.

One of the effects of concentrated glucose solution was thought to be vasodilatation. It seemed very probable that this action could be beneficial to the patient with heart disease, especially with angina pectoris. Hence, concentrated glucose solution became widely popularized in the treatment of angina pectoris. We employed this therapy for more than 30 patients with typical effort angina. The results when critically and carefully followed were never good, and it was noted that several patients developed anginal attacks immediately after the injection of concentrated glucose solution. Severe precordial pain, extreme anxiety, and profuse perspiration were noted, and nitroglycerine was necessary for relief. Other physicians whom we questioned in regard to this matter confirmed our observations, and it was therefore deemed advisable to investigate the effect of hypertonic glucose on the electrocardiogram.

We studied (1) the effect of hypertonic glucose solution, injected intravenously, on the electrocardiogram of patients with effort angina; and (2) the effect of hypertonic glucose solution on the after-exercise electrocardiogram of patients who had cardiac pain on effort.

In a previous paper,¹ we reported the electrocardiographic changes after injecting hypertonic glucose solution in patients with normal hearts and in patients with heart disease but without effort angina. In most instances there was a slight increase in the height of the positive T waves after the injection of hypertonic glucose solution in the patients with normal hearts. However, in a group of fifteen patients with heart disease, but without effort angina, quite different results were obtained. In eight of these cases, in which coronary sclerosis existed, the electrocardiographic changes noted were flattening of an upright T wave or an increase in the depth of an already inverted T wave, and increased depression or elevation of the S-T segment. The patients with rheumatic heart disease in this group presented no electrocardiographic alterations.

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Received for publication April 14, 1939.

I. ELECTROCARDIOGRAPHIC CHANGES AFTER THE INTRAVENOUS INJECTION OF HYPERTONIC GLUCOSE SOLUTION IN PATIENTS WITH ANGINA OF EFFORT

In this group there were fifteen patients, all of whom gave a history of typical cardiac pain on effort. Twelve of the patients had arteriosclerotic heart disease, three of whom also had hypertension, one patient had syphilitic heart disease with insufficiency of the aortic valve, one patient had rheumatic aortic stenosis, and one patient had rheumatic mitral stenosis. In each instance an electrocardiogram was taken first with the patient at complete rest, and then electrocardiograms were taken immediately, five minutes, and, in several instances, ten minutes after the intravenous injection of 50 c.c. of 50 per cent glucose solution. Twelve of the fifteen patients showed marked electrocardiographic changes following the injection of the glucose. Seven of these patients developed some degree of precordial pain, and in two the pain was so severe that nitroglycerine had to be given. The pain in these two instances was associated with marked pallor and profuse perspiration and lasted ten minutes; the nitroglycerine gave prompt relief.

The changes observed were similar to those seen in patients with coronary sclerosis without effort angina but were frequently much more pronounced. In two instances there was a definite increase in heart rate associated with the pain, but this was probably a consequence rather than a cause of the pain, in view of the fact that angina after the injection of glucose was observed without any change in rate. In one case we noted that the heart rate increased only *after* the appearance of precordial pain.

Fig. 1 shows the electrocardiograms of a 54-year-old woman with a history of angina on slight effort and following the ingestion of a heavy meal. Hypertension was also present. The three limb leads are here recorded with the patient at rest (Fig. 1a), and it will be noted that auricular fibrillation and a slight depression of the S-T segments in Leads I and II are present; the latter was due to digitalis. The T waves are upright in all three leads. The beating is irregular, and the rate is 70 per minute. Tracings were taken immediately after 50 c.c. of 50 per cent glucose solution had been given intravenously (Fig. 1b). The patient complained of precordial pain immediately after the injection. The S-T segments in all leads are depressed; this is particularly evident in Lead II. T_3 is now inverted, and the rate is 110 per minute. Tracings were then taken 5 minutes after the injection (Fig. 1c), and it will be noted that the changes are similar to those in Fig. 1b, but less pronounced. The original pattern is evidently returning. The pain was not quite as intense, and the rate diminished to 100 per minute.

The patient had a recurrence of very severe pain about 7 minutes after the injection and broke out into a cold sweat. The next trac-

ings were taken 10 minutes after the initial injection (Fig. 1*d*), and it will be noted that the S-T segments are now more depressed than in Fig. 1*c*. Coincident with the return of pain, it will be noted that the rate increased to 120 per minute.

The same results were obtained when the injection of hypertonic glucose solution was repeated.

Fig. 2 shows the electrocardiograms of a 55-year-old woman with a history of precordial pain of several years' duration, precipitated, as a rule, by effort. Fig. 2*a* was taken with the patient at rest. There is slight depression of the S-T segments in Leads I and II. The cardiac rate is 108 per minute. The next tracing was taken immediately after giving the glucose (Fig. 2*b*). Only 20 c.c. of the solution were given because the needle slipped out of the vein. Note the greater depression of the S-T segment in Lead II, and the appearance of slight displacement in Lead III. At this time the patient complained of slight substernal pain. The rate was 110 per minute.

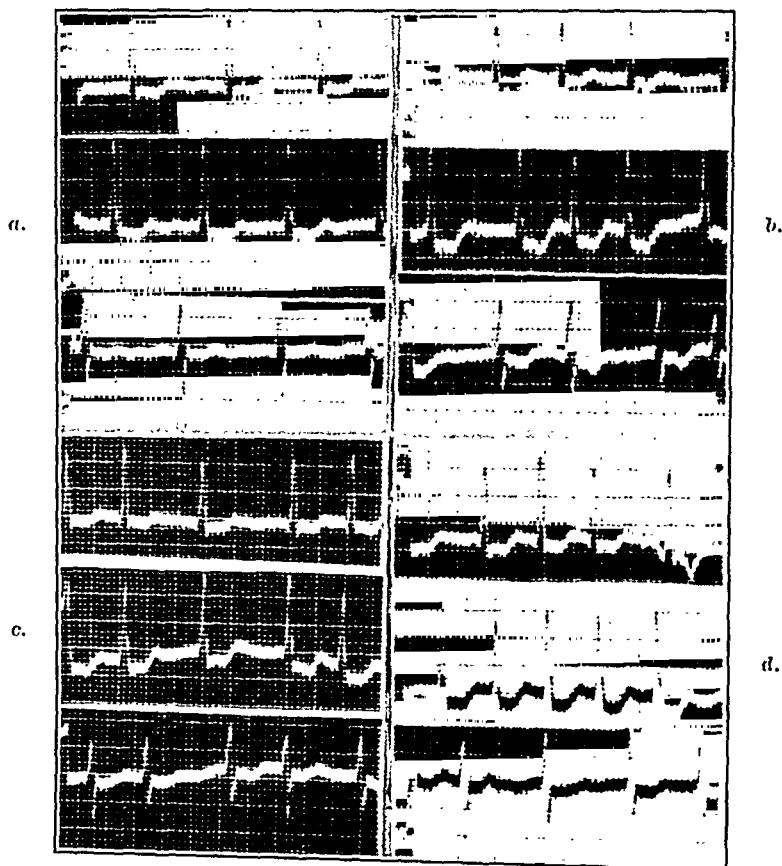


Fig. 1.—Electrocardiograms of a patient, with angina of effort: *a*, before glucose injection; *b*, immediately after glucose injection; *c*, 5 minutes, and *d*, 10 minutes, after glucose injection.

The electrocardiograms in Fig. 3 are those of a 32-year-old woman with a 4-year history of known rheumatic mitral stenosis. She also complained of frequent attacks of precordial pain. The four leads with

the patient at rest are reproduced in Fig. 3*a*. They reveal no abnormality other than a slight diminution of voltage below the normal limits. The cardiac rate at this time was 60 per minute. Hypertonic glucose (50 c.c. of a 50 per cent solution) was then injected intravenously, and electrocardiographic tracings were taken immediately thereafter (Fig. 3*b*). It will be noted that the high, positive T waves in Leads I and II have disappeared. T_1 is now invisible, and in Lead II there is even slight negativity of the T wave. Slight depression of the S-T segment in Lead II is also present. The high, positive T wave in the chest lead (left arm wire to precordial electrode) is changed to a bifid T with a deep, inverted peak. Slight increase in rate, namely, to 75 per minute, and slight substernal discomfort were present. The next tracings were taken 5 minutes after the injection (Fig. 3*c*), and the changes are practically the same as in Fig. 3*b*, although not quite so marked. It will be noted that the rate in Fig. 3*c* is the same as in Fig. 3*a*, and yet pronounced changes are present.

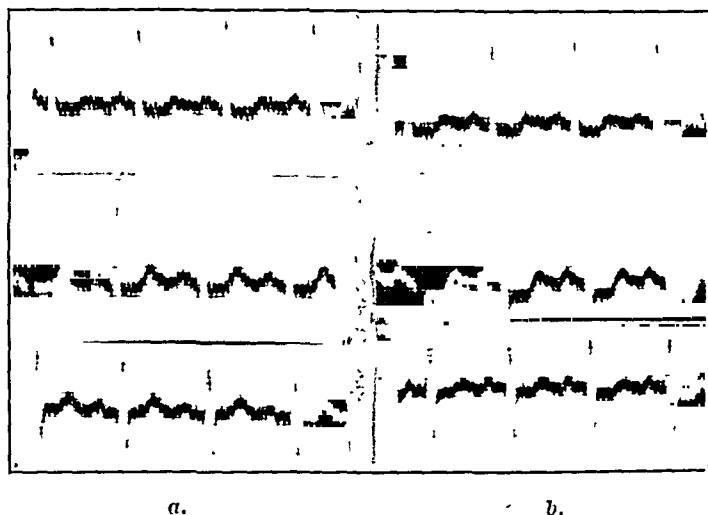


Fig. 2.—This patient also had effort angina. *a*, Before glucose injection; *b*, immediately after the injection of hypertonic glucose solution.

II. THE EFFECT ON THE AFTER-EXERCISE ELECTROCARDIOGRAM OF INJECTING HYPERTONIC GLUCOSE SOLUTION

It was pointed out by one of us, in a series of investigations,^{2, 3} that registration of the electrocardiogram after exercise can render considerable help in the diagnosis of coronary artery disease. In patients who complain of angina on effort there is usually stenosis of a coronary artery, either because of sclerosis of the vessel or syphilitic narrowing of its ostium. When these patients are at rest the blood supply to the heart can be sufficient despite the stenosis, pain is absent, and the electrocardiogram may be normal. After exercise, which is graded according to the condition of the patient and never exceeds the amount that the patient engages in many times during the course of the day of his own accord, the blood supply to the heart becomes insufficient, and the

electrocardiogram presents marked changes. Pain can, but need not, appear. If the same patient exercises immediately after taking nitroglycerine, these electrocardiographic changes do not present themselves. Other vasodilators, injected intravenously, can also prevent these electrocardiographic changes or diminish the degree of the changes.

One would expect that the after-exercise electrocardiogram, taken immediately after the injection of hypertonic glucose solution in patients with coronary stenosis, would show less change if glucose has a definitely dilating effect on the coronary arteries.

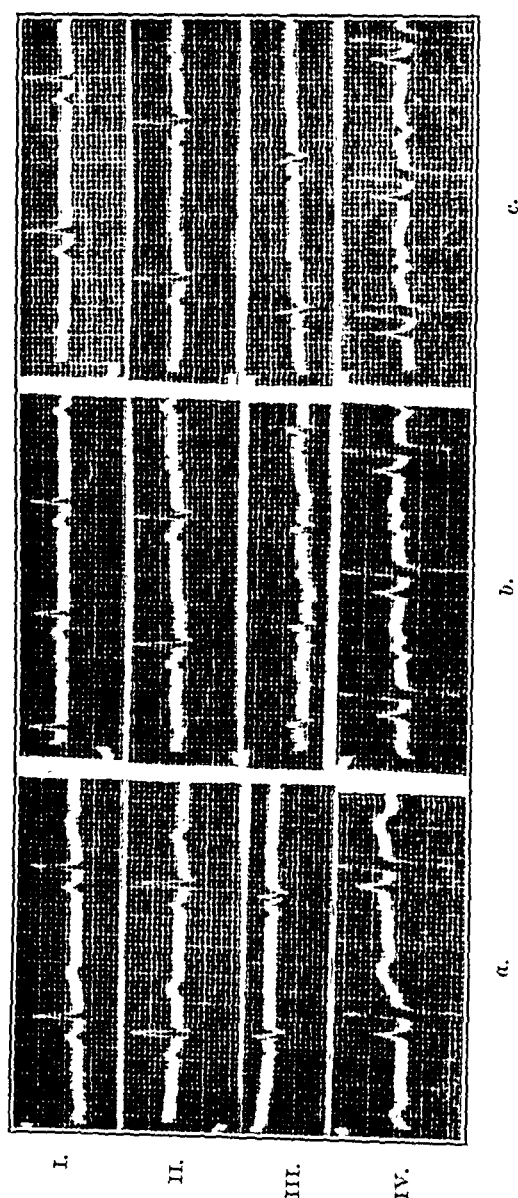


Fig. 3.—Electrocardiograms of a patient with mitral stenosis and attacks of precordial pain. *a*, Before glucose injection; *b*, immediately, and *c*, 5 minutes, after the injection of glucose.

This investigation was carried out in seventeen cases. All patients had angina of effort and either coronary sclerosis or syphilitic aortitis. The attacks were typical, and nitrites worked promptly in all. Under

constant conditions, an exercise test was carried out first in all cases. The electrocardiogram was recorded before the exercise and immediately after, as well as 2, 5 and, oftentimes, 10 minutes afterward. Several repetitions showed that the exercise reaction was always the same. Forty cubic centimeters of a 40 per cent glucose solution were then given intravenously, and, 5 minutes later, after the same amount of work, electrocardiograms were taken in the same fashion.

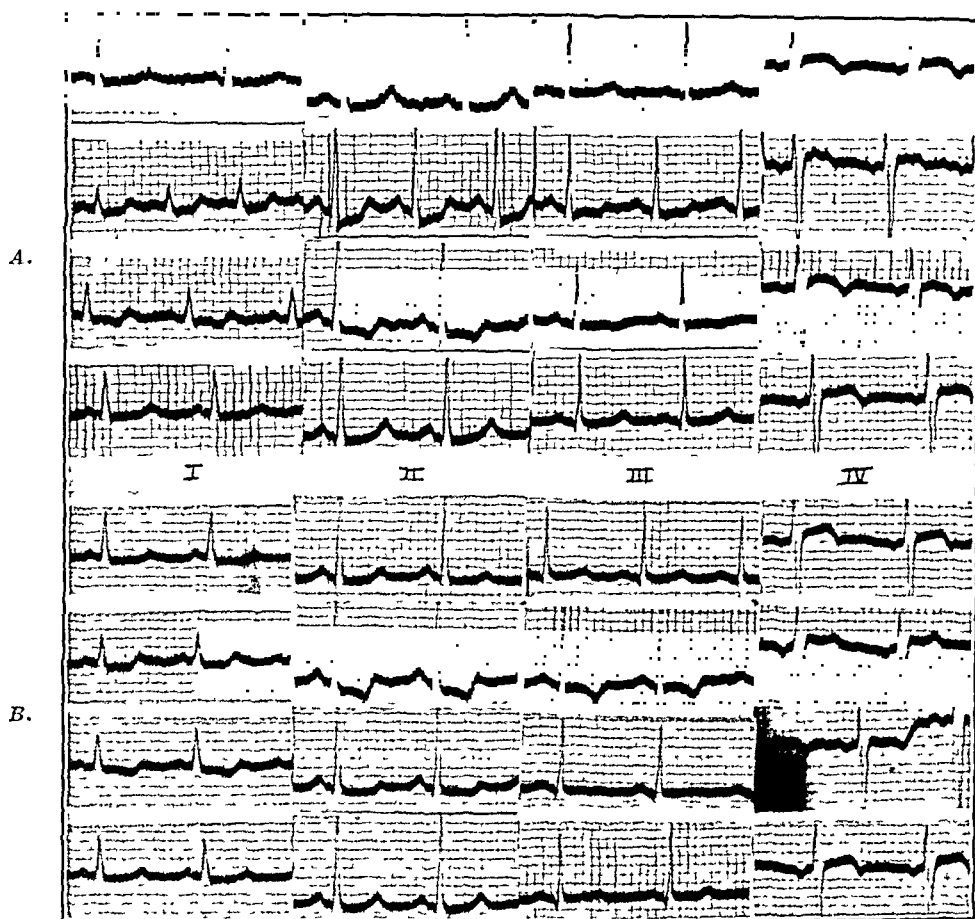


Fig. 4A.—Electrocardiograms of a patient with aortic insufficiency. Before exercise (top row), and following exercise (lower 3 rows).

Fig. 4B.—Same patient as 4A. Electrocardiogram 5 minutes after injection of glucose with the patient at rest (top row), and after exercise (lower 3 rows).

✓ In twelve of the seventeen cases, the electrocardiogram showed pathologic alterations after exercise, namely, depression of the S-T segments and abnormal T waves. In two cases the results were questionable, and in three cases the electrocardiograms after effort showed only the familiar physiologic changes. ✓ After the injection of glucose, the alterations in the electrocardiogram after exercise were unquestionably accentuated, and they occurred in all cases. In seven cases the reaction to exercise after the injection was worse than before. Never was the reaction less pronounced. These results are illustrated in Figs. 4 and 5.

Fig. 4 is from a 34-year-old patient with insufficiency of the aortic valve, the etiology of which could not be established with certainty; it was probably syphilitic. The patient suffered severe anginal attacks which were promptly relieved by nitroglycerine. The after-exercise electrocardiogram, which was recorded many times, became immediately positive, and showed the same changes that occurred in spontaneous attacks while at rest during a hypertensive crisis.

In Fig. 4a we see the three limb leads and chest leads (left leg wire to the area of absolute heart dullness to the left of the sternum) next to each other. The uppermost row of curves shows the resting electrocardiogram, in which the only item of note is the low T wave in Lead I. No significant changes are present. Two minutes after the exercise test (second row), there appears a definite depression of the S-T segment in Lead I, the T waves in Leads II and III are deeply negative, and in the chest lead the slightly negative T after the elevated S-T segment is changed to a positive T. After 5 minutes (third series), the changes are less marked. After 10 minutes (lowest series), the original pattern has returned. The time necessary for the changes to disappear varied from patient to patient; in some cases it was from 20 to 40 minutes.

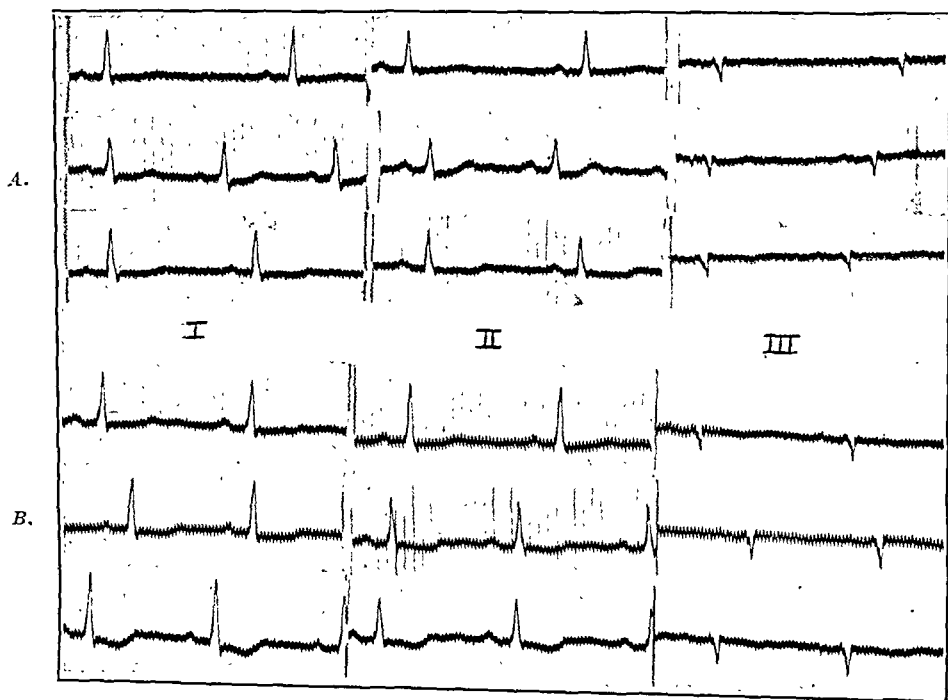


Fig. 5A.—This patient had coronary sclerosis with angina of effort. The first row before exercise, and the next 2 rows after exercise.

Fig. 5B.—Same patient as 5A. First row electrocardiogram before exercise, 5 minutes after injection of glucose. Second and third rows, after exercise.

Fig. 4b shows the results of an exercise test 5 minutes after the injection of 40 c.c. of 40 per cent glucose solution. The resting electrocardiogram has the same appearance as that in Fig. 4a. The same

changes appear after the exercise as in the previous experiment, and the time necessary for them to disappear is also the same. Upon repeating the experiment several days later, the results were identical.

Fig. 5 is from a 63-year-old patient with coronary sclerosis and angina of effort. The T wave is absent in Lead I and is hardly visible in Lead II. Immediately after the exercise test, high, normal T waves appeared (not illustrated). This is a normal exercise reaction and depends upon increased sympathetic tonus. After 2 minutes (second series), a definite depression of the S-T segment appeared. However, this does not exceed normal limits, and the T waves are more nearly normal than they were before the exercise. Five minutes after the exercise test we see in the lowest series a definite depression of the S-T segments, this time in all leads and unquestionably of abnormal degree.

On the next day, 2 minutes after exercise, and 5 minutes after the injection of hypertonic glucose solution (Fig. 5*b*), the depression of the S-T segment was more marked than in Fig. 5*a*, and the height of the T wave was less. Five minutes after exercise (lowest series), an even more marked change than in Fig. 5*a* appeared. The pain reaction after exercise was greater than on the previous day, when glucose had not been injected.

DISCUSSION

Several theories have been advanced to explain the beneficial effects of glucose upon the heart. The following, especially, require consideration:

1. There is improvement of the nutrition of the heart by direct action of the glucose on the muscle fibers.
2. Dilatation of the coronary arteries is brought about by direct alteration of the physical properties of the cells.
3. An increase of the coronary blood flow is produced by other indirect mechanisms. ✓

1.—It has long been assumed that one of the reasons for failure of the heart was that its nutritive supply, especially its store of carbohydrate, was diminished. In animal experiments it has been shown that glucose is necessary for cardiac efficiency.⁴ Although adequate proof was lacking, it was easy to infer that the failing heart might be deprived of, or could not utilize, combustible carbohydrate.

It has been frequently recommended that carbohydrate be given by mouth in the treatment of patients with heart disease,⁵⁻⁹ in order to improve the nutrition of the heart. For the past twenty years glucose has also been used intravenously with many favorable results. It has been recommended in amounts varying from 20 to 200 c.c. and in concentrations ranging from 20 to 50 per cent.^{10, 11}

However, despite the many reports favoring the use of glucose to improve cardiac nutrition, it has certainly not been proved that glu-

cose actually accomplishes this. The improved efficiency noted in the heart-lung preparation of Bayliss and co-workers⁴ does not necessarily mean that the human heart will respond in the same way, since one cannot apply too fully results obtained on the heart of the experimental animal under unnatural conditions to the heart of the human subject. The problem of the effect of hypertonic glucose on the heart seems to be more intimately related to coronary blood flow.

2.—A widely accepted theory of the action of hypertonic glucose assumes a direct effect upon the vessel wall. The physical properties of the muscle cells in the walls of the coronary arteries are supposed to be altered by virtue of osmotic and colloidoclastic effects.^{12, 13} The colloidoclastic effect is presumed to cause a temporary change in the quality of the blood and tissue colloids. In this way, or through osmotic effects, a dilatation of the coronary arteries should take place.

In animal experiments, using the Morawitz cannula, Salomon¹³ employed a 20 per cent glucose solution and reported a direct dilating effect upon the coronary arteries. He observed this phenomenon in thirty-seven out of forty-four animals. For clinical use he advocated more concentrated solutions.

3.—Ginsberg, Stoland, and Loy¹⁴ found that in the intact animal (dog) 10 c.c. of a 50 per cent dextrose solution increased the coronary circulation from 10 to 100 per cent, or more, and that the increased rate of flow was maintained for 40 minutes, or more. The increase occurred in the absence of tachycardia and without a rise in blood pressure, and it was independent of neurogenic mechanisms. Hypertonic saline solution did not produce as marked an increase of flow as hypertonic glucose solution. The height of the blood sugar was unrelated to the amount of coronary blood flow. In six heart-lung preparations these authors failed to observe vasodilatation and hence concluded that glucose does not have a direct effect upon the vessel wall. Hydremia was probably the most important factor in increasing the coronary blood flow, despite the fact that the specific gravity and viscosity of the blood quickly returned to normal, while the augmented flow through the coronary vessels continued.

Frey and Hess¹⁵ performed a series of experiments similar to those of Ginsberg, et al., but they used the "thermostromuhr" to measure the coronary blood flow. They employed 10 c.c. of a 50 per cent glucose solution and noted that, in some animals, they obtained a rapid, marked dilatation of the coronary vessels. In other animals, however, they observed only a slight dilatation, while in still other instances, a diminution of blood flow occurred. In 61 per cent of the cases an augmentation of blood flow occurred, whereas in 26 per cent of the cases an actual diminution of flow was observed. The blood pressure remained unchanged after the introduction of the glucose. These

authors discuss the possibility that glucose acts on the adrenalin-insulin mechanism and, in this way, produces alterations of the flow of blood through the coronary arteries.

It has long been known that hypertonic glucose solution exerts a marked osmotic effect when introduced into the blood stream.¹⁶⁻¹⁹ In the presence of normally functioning coronary vessels, the plethora produced by the injection of hypertonic glucose solution may contribute to the increased blood flow. Changes in blood pressure and cardiac rate cannot play a role, since, as has been pointed out by several authors, the pressure and rate are unaffected by the injection of hypertonic glucose solution. It is important to correlate these facts, as will be pointed out later.

Little need be said regarding the possible dilating effect of glucose upon the smaller coronary vessels. It has been suggested that glucose can dilate coronary vessels, like some known vasodilators, by vagal inhibition or sympathetic stimulation. The action of glucose, however, is entirely independent of nerve supply.¹⁴

From an extensive review of the literature, Martin²⁰ concludes that hypertonic glucose solution, given intravenously, improves the coronary blood flow and increases the venous return and cardiac output.

Judging from the foregoing remarks, there would seem to be a definite rationale for the use of hypertonic glucose solution in the treatment of those forms of heart disease associated with diminution in coronary blood flow. Many observers have reported that favorable results in the treatment of angina pectoris and congestive heart failure were obtained by using hypertonic glucose solution in varying amounts and concentrations.²¹⁻²⁵ Some authors advised the use of insulin with the hypertonic glucose solution.¹¹ Critical appraisal, however, of the literature does not warrant too optimistic an opinion with regard to the belief that hypertonic glucose solution is beneficial in coronary artery disease. Scattered through many reports one finds evidence that precordial pain occasionally developed during treatment,²⁴⁻²⁶ and the objective results often do not warrant the conclusions drawn.

There is a question whether or not T-wave alterations always indicate myocardial damage.²⁷ A positive T wave may actually be increased in height in the presence of a definite myocardial lesion, and it has not been proved that in every instance an inverted T wave means myocardial injury. Of much greater importance, however, is the association of cardiac pain with inversion of the T waves after the glucose injection. This must invariably mean myocardial impairment, since seven patients developed precordial pain. Hence, glucose in hypertonic concentration is harmful and alters the ratio of blood supply to the oxygen demand of the myocardium. This statement is

also borne out by the fact that seven of seventeen patients with effort angina developed more intense pain after exercise when hypertonic glucose solution had been given previously.

In practically all of our cases in which there was reason to believe that the coronary arteries were sclerosed, definitely abnormal changes appeared in the electrocardiogram, but, as previously reported,¹ in the cases of rheumatic valvular lesions, and in patients with hypertension whose coronary arteries were probably intact and patent, no electrocardiographic changes were noted.

In one case of mitral stenosis in which there was precordial pain, marked changes in the T wave were observed (Fig. 3b) after the injection of hypertonic glucose solution. During an attack of anginal pain, patients with mitral stenosis frequently have abnormal electrocardiograms.³ There is reason to believe that, since cardiac hypertrophy exists, and the stroke volume is small, myocardial ischemia results when the work of the heart is increased without a proportionate augmentation of the coronary blood flow. Patients with severe rheumatic involvement of the aortic valve may, however, show no changes. In one case of rheumatic stenosis of the aortic valve no alteration of the electrocardiogram occurred after the injection of hypertonic glucose solution, and yet this patient had severe effort angina. At autopsy, stenosis of the aortic valve was found, but the coronary vessels were entirely free of sclerosis.

✓ It is apparently true that glucose dilates the coronary vessels in experimental animals, although contradictory findings have been reported,¹⁵ but an increased blood flow to an organ does not necessarily indicate increased oxygenation. An increased velocity of blood flow may diminish the utilization of oxygen, for, because of the rapid transit of blood through the smaller vessels, oxygen cannot be removed quickly enough by the tissues. When total blood flow is increased, the capillary flow is often not comparably augmented because of short circuiting. Frequently, in cases of arteriosclerosis obliterans of the lower extremities, if the venous channels are tapped the blood will be found to be well oxygenated, indicating failure of oxygen utilization. Moreover, sclerotic vessels may fail to show the same dilatation as the healthy vessels of the experimental animal. Under such conditions anoxia results, since the blood volume is increased, the stroke volume is greater after the intravenous injection of glucose, and the oxygen requirement becomes greater without a comparable increase in coronary blood flow.

It was found²⁸ that after the intra-arterial injection of hypertonic salt solution there was a diminished oxygen utilization in the tissues. This phenomenon was believed to be caused by a change in the vessel wall between tissue and blood which prevented the oxygen from being given up. This explanation may be applicable to the action of hypertonic glucose solution on the coronary circulation, for, despite increased

blood flow brought about by intravenously injected hypertonic solutions, the oxygen supply to the tissue may actually be diminished because of failure of utilization.

Although an increased cardiac rate was observed in some of our patients, this could not play a role in the production of pain after the injection of glucose, since we have observed the same electrocardiographic changes without any change in rate whatsoever. We are inclined to believe that any increase in cardiac rate was the result, rather than the cause, of the pain.

One of the possible explanations for the cardiac pain which deserves consideration is that the glucose may have stimulated the secretion of insulin. Insulin has been shown to produce changes in the T wave²⁹ and may even precipitate cardiac pain. Glucose is one of the best agents for stimulating the production of insulin and has been called the insulin hormone.^{30*} Curves have been plotted to show that hypertonic glucose solution stimulates the production of insulin.³¹ This being the case, it would seem possible that the cardiac pain which the patients developed after the injection of hypertonic glucose solution was an insulin effect.

There are certain observations which indicate that insulin has no direct action on the coronary vessels. In the first place, there is no parallelism between the height of the blood sugar and any electrocardiographic alterations. Marked electrocardiographic changes have been observed before hypoglycemic levels were reached. In the second place, there are many observations which prove that the hyperadrenalinemia accompanying the fall of blood sugar produces the changes. Even if insulin has a direct action on the coronary vessels it is probably secreted in too small an amount to cause spasm.

Investigations are now under way to determine whether hypertonic saline and hypertonic sucrose solutions can produce the same changes as hypertonic glucose solution. It is necessary to ascertain whether the results with glucose are specific, i.e., whether the results depend upon the concentration or the nature of the injected substance.

In conclusion, we wish to point out that the beneficial effects of intravenously injected hypertonic glucose solution upon the heart are very questionable. That it has a marked osmotic effect in pulmonary edema, cerebral edema, and in cases of increased intraspinal pressure cannot be denied, but it is questionable whether or not hypertonic glucose solution has any place in the treatment of coronary artery disease. It has been shown to cause severe angina and, therefore, may be deleterious. It should be used cautiously in patients with coronary sclerosis, and if it is to be used at all (pulmonary edema), we recommend that it be used in conjunction with vasodilators, such as nitroglycerine.

*This has also been denied.³²

SUMMARY

In two series of cases we studied the effect on the heart of the intravenous injection of hypertonic glucose solution. In Group I it was observed that in patients with effort angina and coronary arteriosclerosis the injection of hypertonic glucose solution produced marked electrocardiographic changes and frequently caused pain. In Group II it was observed that patients with effort angina and pathologic alterations of the electrocardiogram after exercise developed the same, and even more marked, alterations of the electrocardiogram when hypertonic glucose solution was given shortly before the performance of the exercise test.

The various theories concerning the effect of hypertonic glucose solution on the blood and coronary arteries were discussed, and the possible causes for the production of cardiac pain after the injection of hypertonic glucose solution were reviewed.

Since the submission of this paper for publication there has appeared, in the May, 1939, issue of this JOURNAL, an article by L. B. Ellis and J. M. Faulkner on the circulatory effects of 50 per cent dextrose and sucrose solutions on patients with heart disease. The authors cautioned that the increase of plasma volume which attends the injection throws an extra load on the circulation similar to that caused by the injection of large amounts of fluid in patients whose circulatory balance is already precarious.

We wish to express appreciation to Miss Mover and Miss Pringle for technical assistance.

REFERENCES

1. Scherf, D., and Weissberg, J.: The Influence of Hypertonic Glucose on the Heart, New York, M. Coll. & Flower Hosp. Bull. 2: 41, 1939.
2. Hausner, E., and Scherf, D.: Über Angina pectoris Probleme, Ztschr. f. klin. Med. 126: 166, 1933.
3. Scherf, D., and Goldhammer, S.: Zur Frühdiagnose der Angina pectoris mit Hilfe des Elektrokardiogramms, Ztschr. f. klin. Med. 124: 111, 1933.
4. Bayliss, L. E., Müller, E. A., and Starling, E. H.: The Action of Insulin and Sugar on the Respiratory Quotient and Metabolism of the Heart-Lung Preparation, J. Physiol. 65: 33, 1928.
5. Goulston, A.: West Indian Cane Sugar in the Treatment of Certain Forms of Heart Disease, Brit. M. J. 2: 693, 1912.
6. Soca, F.: Angina Pectoris (editorial), J. A. M. A. 65: 2,166, 1915.
7. Hyman, A. S., and Protas, M.: Diet in Heart Disease—The Role of High Carbohydrate Feeding, New York State J. Med. 28: 716, 1928.
8. Smith, K. S.: The Nutrition of the Heart in Relation to the Electrocardiogram and Anginal Pain, Lancet 1: 632, 1933.
9. Smith, K. S.: Insulin and Glucose in the Treatment of Heart Disease, Brit. M. J. 1: 693, 1933.
10. Büdingen, T.: Die Anwendung hypertotonischer Traubenzuckerlösungen bei organischen Herzerkrankungen, Klin. Wchnschr. 2: 169, 1923.
11. Root, H. F., and Graybiel, A.: Angina Pectoris and Diabetes Mellitus, J. A. M. A. 96: 925, 1931.
12. Handovsky, H., and Meyer, E.: Experimentelle Untersuchungen über die Wirkung des Traubenzuckers auf Blutgefäße, Klin. Wchnschr. 2: 82, 1923.
13. Salomon, H.: Über den Einfluss des Traubenzuckers auf Herzvolumen, Coronarweite und Pulsfrequenz des Säugetierherzens, Arch. internat. de pharmacodyn. et de therap. 49: 445, 1935.

14. Ginsberg, A. M., Stoland, O. O., and Loy, D. T.: Studies on the Coronary Circulation. III. Effect of Intravenous Injections of Dextrose on the Coronary Circulation, *Arch. Int. Med.* 55: 42, 1935.
15. Frey, J., and Hess, W.: Die Kranzaderdurchblutung bei Anwendung einiger neuer gefässerweiternder Stoffe, *Klin. Wchnschr.* 16: 1,642, 1937.
16. Erlanger, J., and Woodyatt, R. T.: Intravenous Glucose Injections in Shock, *J. A. M. A.* 69: 1,410, 1917.
17. Kinsman, J. M., Spurling, R. G., and Jelsma, F.: Blood and Cerebro-Spinal Fluid Changes After Intravenous Injection of Hypertonic Solutions, *Am. J. Physiol.* 84: 165, 1928.
18. Litchfield, L.: Glucose Intravenously as a Therapeutic Measure, *J. A. M. A.* 71: 503, 1918.
19. Weed, L. H., and McKibben, P. S.: Pressure Changes in the Cerebro-Spinal Fluid Following Intravenous Injections of Solutions of Various Concentrations, *Am. J. Physiol.* 48: 512, 1919.
20. Martin, E.: *Dextrose Therapy in Everyday Practice*, New York, 1937, Paul B. Hoeber, Inc.
21. Korbsch, R.: Zur intravenösen Injektion hochprozentiger Traubenzuckerlösungen, *Deutsche med. Wchnschr.* 47: 332, 1921.
22. Hassencamp, E.: Die Behandlung der Angina pectoris mit Traubenzucker, *Ztschr. f. Kreislaufforsch.* 23: 132, 1931.
23. Müller-Deham, A.: Eine zweckmässige Kombinationstherapie bei intermittierendem Hinken und Angina pectoris, *Deutsche med. Wchnschr.* 54: 2,052, 1928.
24. Sprague, H. B., and Camp, P. D.: Intravenous Hypertonic Glucose in the Treatment of Cardiac Disease—preliminary report, *New England J. Med.* 206: 288, 1932.
25. Smith, A. E., and Luten, D.: Study of Glucose Therapy in Heart Failure in Advanced Cardiac Disease, *AM. HEART J.* 9: 437, 1934.
26. Feinberg, S. C.: The Treatment of Coronary Artery Disease by Intravenous Injections of Hypertonic Saline Solution, *Am. J. M. Sc.* 191: 410, 1935.
- ✓ 27. Katz, L. N.: The Significance of the T Wave in the Electrogram and Electrocardiogram, *Physiol. Rev.* 8: 447, 1928.
28. Klein, O.: Zur Frage der Störung des inneren Gaswechsels, *Wien. klin. Wchnschr.* 50: 467, 1937.
29. Edwards, D. J., and Page, I. H.: Observations on the Circulation During Hypo-Glycemia From Large Doses of Insulin, *Am. J. Physiol.* 69: 177, 1924.
30. Grafe, E., and Meythaler, F.: Beitrag zur Kenntnis der Regulation der Insulinproduktion; der Traubenzucker als Hormon für die Insulinabgabe, *Arch. f. exper. Path. u. Pharmakol.* 125: 181, 1927.
31. Lennox, W. G.: Stimulation of the Sugar-Regulating Mechanism as Shown by Duplicate Blood Sugar Curves, *J. Biol. Chem.* 73: 332, 1921.
32. Geiger, E.: Traubenzucker als Hormon der Insulinsekretion? *Klin. Wchnschr.* 6: 2,000, 1927.

DEPROTEINATED PANCREATIC EXTRACT (DEPROPANEX)

1. EFFECT IN THE TREATMENT OF INTERMITTENT CLAUDICATION DUE TO ARTERIOSCLEROSIS OBLITERANS

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INTEREST in the therapeutic use of various tissue extracts was stimulated by the work of Frey and Kraut (1926), who prepared and studied a pancreatic extract, kallekrein (later called padutin). It was reported to inhibit the crural pain causing intermittent claudication. Wolffe, Findlay, and Dessen (1931)^{2, 3} described extracts of pancreatic tissue which gave therapeutically similar results. Schwarzmenn (1930)⁴ reported improvement following the use of skeletal-muscle extract in three patients with intermittent claudication. Nuzum and Elliot (1931)⁵ were unable to demonstrate vasodilatation in animals after intramuscular or subcutaneous injection of kallekrein. Barker, Brown, and Roth (1935)⁶ found intermittent claudication present in 90 per cent of their patients with peripheral arterial disease. They noted a definite lessening of this symptom following the use of a pancreatic tissue extract. One of the present authors⁷ reported similar results from our clinic in 1935. The substances used in the above studies produced pain and sometimes redness and swelling at the site of injection. Mild systemic reactions, including slight chilliness and fever, occasionally occurred.

DEPROTEINATED PANCREATIC EXTRACT (DEPROPANEX)

Following suggestions made by members of this clinic, and others, the Sharp and Dohme Laboratories undertook to refine and fractionate extract #568. Deproteinized pancreatic extract represents one of these fractions.

It is a colorless, saline solution of a chemically purified, protein-free, nitrogenous fraction, derived from an acid-alcohol extract of beef pancreas. Physiologic tests show that it is free from insulin, histamine, and acetylcholine. It contains approximately 2.5 per cent of solids, including 0.25 per cent of nonprotein nitrogen, 0.9 per cent of sodium chloride, and 0.25 per cent of phenol as a preservative. It is adjusted to a pH of 6.5 to 6.8.

It is assayed by comparing its effect with that of a standard preparation on the arterial blood pressure of anesthetized dogs. This standard preparation is of such potency that 1 c.c., in a large series of dogs, gives an average lowering of arterial blood pressure equivalent to the rise in arterial blood pressure produced by 0.01 mg.

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Aided by a grant from Sharp and Dohme, Inc.

Received for publication April 5, 1939.

of epinephrine in the same dogs. The standard is preserved by the lyophile process, and stored in the dried state at 5° C. Each new lot of deproteinized pancreatic extract is standardized by comparing its depressor effect with that of a solution of the standard preparation on the normal and atropinized dog. The physiologic action of each lot is also studied by means of the heart-blocking effect in mice. Two cubic centimeters of depropanex are injected into white, female mice, and an electrocardiograph is used to ascertain whether heart block occurs. The material is injected intraperitoneally and should not cause death from heart block in any of at least three mice within fifteen minutes. Its depressor action in urethanized rabbits is also noted.

INTERMITTENT CLAUDICATION

The term intermittent claudication, as used in this report, may be defined as limping due to a pain or cramplike sensation, or as a sense of extreme fatigue most commonly localized in the calf, thigh, or foot muscles, induced by a limited amount of walking or other leg effort. This may be so severe as to prevent continued action of the group of muscles involved. A similar phenomenon may occur in other muscle groups under unusual conditions. Muscle spasm or muscle failure severe enough to cause the subject to fall may occur if exercise is continued. The pain or disagreeable sensation is usually relieved within a few minutes by cessation of muscular effort, frequently without change in position. The symptoms are not considered typical if they occur during rest. The amount of muscular effort necessary to produce this syndrome is fairly constant in most individuals during any one phase of the disease which causes it. Weather, environmental temperature conditions, and complicating illnesses may bring about some fluctuation in this regard. For more than five years we have been studying the effects of various pancreatic and heart-tissue extracts on this syndrome, and during the past year we have used deproteinized pancreatic extract in these studies.

METHOD

A. Apparatus.—In order to evaluate the effects of these extracts, we have found it essential to use a method of measuring the amount of work per unit of time necessary to produce this syndrome. Certain previous workers⁶ depended on measuring timed walking. Landis, et al.,⁸ used an ergometer, the muscle contractions being rhythmically induced by a faradic current applied to the leg. Berry,* at our clinic, devised a vertical stand fitted with a foot pedal which, when depressed, raises a weight of 13.6 pounds (Fig. 1). The patient stands upright on this apparatus in the same position in which he normally walks, with the foot of the extremity to be tested on the pedal. The other foot is placed on an adjoining platform. He grasps the upper bar with his hands to maintain his balance. The entire foot is kept on the pedal, and as the anterior portion of the foot is depressed to lift the weight the muscles of the leg used in walking are brought into play. The patient is paced at 120 steps per minute with a stop watch or metronome, and he is not allowed to stop until the pain, cramp, or fatigue in the calf or thigh becomes so severe that he is unable to continue.

*Dr. Maxwell Berry, now Fellow, Mayo Clinic, Rochester, Minn.

This method of measuring claudication time quite satisfactorily maintains, as a constant, the work done per minute by the muscles being tested. Care must be exercised that other sets of muscles are not thrown into action when the fatigue syndrome begins. This can be practically prevented by having the patient maintain an unchanged position on the apparatus. The room temperature should be kept constant. In our experiments, a temperature of $20^{\circ} \pm 1^{\circ}$ C. was used. This test is convenient in that it takes a relatively short time to produce the syndrome.

B. Procedure.—The patient rested by sitting for one-half hour after reporting to the examiner. The first control test was performed, and, following another rest of one-half hour's duration, a second control test was made. The times for these two tests were in most instances very nearly identical. Three cubic centimeters of the extract to be tested were injected intramuscularly after the second test. One-half hour later a third test was made.

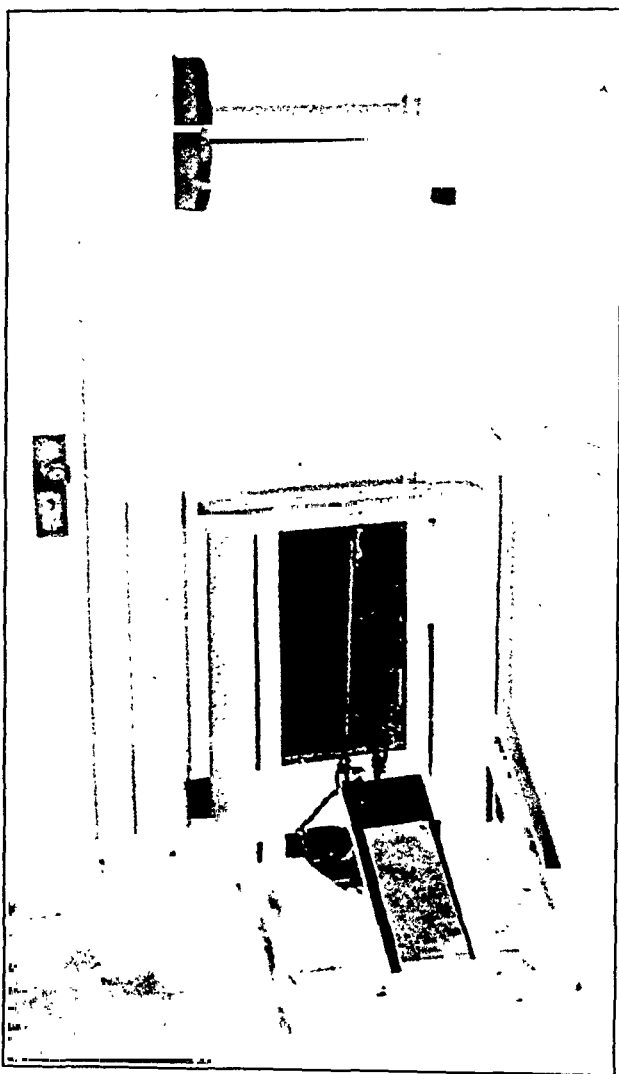


Fig. 1.

Using the above technique, the effect of deproteinated pancreatic extract was determined in twenty-seven patients with definite arteriosclerotic disease of the vessels of the lower extremities. Each patient was carefully studied by means of

oscillometric readings, roentgenograms, arteriograms, and other procedures, as indicated. They were all ambulatory. None had gangrenous lesions. After the original tests, the treatment consisted of 3 c.c. of the deproteinized pancreatic extract intramuscularly triweekly. The tests were rechecked frequently. Patients have now been followed as long as nine months. During the course of treatment each patient received, on one or more occasions, without his or her knowledge, 3 c.c. of physiologic salt solution as a control. An identical test was performed one-half hour after the saline was given. As stated above, deproteinized pancreatic extract is colorless, and, when injected intramuscularly, it causes no more pain than saline.

The ages of the patients varied from 50 to 80 years, the average being 62 years. There were twenty-four males and three females. All were white. Ten were Hebrew. Thirteen had received no previous treatment for their vascular disease. Fourteen had received previous treatment, such as other tissue extracts, suction-pressure, or intermittent venous occlusion. Such treatment was discontinued before the original tests with the pancreatic extract now being studied were made. All of the patients were advised not to use tobacco, and were instructed to take warm foot baths nightly, wear warm socks and proper shoes, and take proper care of the nails and corns.

RESULTS

The tables (Nos. I, II, and III) show the results obtained. Table I lists eight patients with untreated, uncomplicated, arteriosclerotic vascular disease. Six showed improvement, and two, no improvement, with the initial tests. All of those receiving ten or more treatments were benefited.

Table II lists five patients, untreated, but with complicating diabetes, heart disease, varicose veins, or other abnormalities which might have had a relationship to this condition. Four showed improvement, and one, no improvement, with the initial tests. The four were improved after ten or more treatments. The one patient who was not benefited by the initial dose was not treated.

Table II lists fourteen patients who had been treated previously by other means, and includes patients both with and without complicating diseases. Thirteen of these showed improvement after the initial test. In one instance (14) the benefit was so slight as to be inconsequential. Ten individuals received ten or more treatments, and all of these showed improvement.

The saline which was used as a control produced results of no significance in these series.

Table IV summarizes the first three tables. The initial claudication time varied from an average of 1' 26" to 1' 43" in these groups, with extremes of 35" and 2' 30". All tests were discontinued if claudication had not developed within 5 minutes. The actual averages are, therefore, greater than the averages given whenever so indicated in this table. One-half hour after the initial 3 c.c. of deproteinized pancreatic extract, the average claudication time for all patients was greater than 3' 1", an increase of about 100 per cent. This gain was

temporary with the first few injections. Nineteen who received ten or more treatments showed an average claudication time of more than 4' 19", an increase of nearly 300 per cent. The average control claudication time for twenty-four patients tested with normal saline was over 2' 15" (these patients had had some previous treatment), and after saline it was more than 2' 18". There was, therefore, no significant change.

TABLE I

EFFECT OF 3 C.C. OF DEPROTEINATED PANCREATIC EXTRACT ON THE CLAUDICATION TIME IN 8 PREVIOUSLY UNTREATED PATIENTS WITH UNCOMPLICATED ARTERIOSCLEROTIC VASCULAR DISEASE

IMMEDIATE RESPONSE			SALINE CONTROLS*		AFTER 10 OR MORE TREATMENTS
Case No.	Average time before DPX	One-half hr. after DPX	Average time before saline	One-half hr. after saline	Average claudication time
1	1' 48"	No claud. in 5 min.	2' 30"	2' 30"	-----
5	44"	1' 33"	1' 19"	56"	1' 39"
6	2' 37"	1' 44"	No claud. in 5 min.	No claud. in 5 min.	No claud. in 5 min.
24	1'	1'	43"	52"	No claud. in 5 min.
31	1' 30"	3' 4"	No claud. in 5 min.	No claud. in 5 min.	No claud. in 5 min.
37	1' 56"	4' 32"	2' 15"	51"	-----
39	1' 11"	No claud. in 5 min.	4' 40"	No claud. in 5 min.	No claud. in 5 min.
43	59"	1' 36"	-----	-----	-----

*Most of these tests were made after a week or more of treatment.

TABLE II

EFFECT OF 3 C.C. OF DEPROTEINATED PANCREATIC EXTRACT ON THE CLAUDICATION TIME IN 5 PREVIOUSLY UNTREATED PATIENTS WITH ARTERIOSCLEROTIC VASCULAR DISEASE AND OTHER COMPLICATING CONDITIONS

IMMEDIATE RESPONSE			SALINE CONTROLS*		AFTER 10 OR MORE TREATMENTS
Case No.	Average time before DPX	One-half hr. after DPX	Average time before saline	One-half hr. after saline	Average claudication time
2	1' 55"	3' 14"	1' 16"	1' 47"	No claud. in 5 min.
4	1' 34"	No claud. in 5 min.	1' 43"	2' 30"	No claud. in 5 min.
26	1' 20"	1' 14"	1'	47"	1' 37"
34	1' 23"	3' 30"	2' 37"	2' 37"	4' 56"
35	2' 22"	No claud. in 5 min.	-----	-----	-----

*Most of these tests were made after a week or more of treatment.

A record was kept of how far the patients had to walk to produce this syndrome before and during treatment (New York City blocks). The average number of blocks for the entire group before treatment was about two. The average after ten or more treatments was about eight, an increase of 400 per cent (compare with the 300 per cent improvement as measured by the apparatus).

An attempt was made to correlate the claudication time with the oscillometric readings. As one would expect, it was generally true that the lower the oscillometric readings, the shorter the claudication time and the slower the response to therapy.

TABLE III

EFFECT OF 3 C.C. OF DEPROTEINATED PANCREATIC EXTRACT ON THE CLAUDICATION TIME IN 14 PATIENTS WITH ARTERIOSCLEROTIC VASCULAR DISEASE, ALL OF WHOM HAD BEEN TREATED PREVIOUSLY BY OTHER MEANS. SOME OF THE PATIENTS HAD COMPLICATING DISEASES, AND SOME HAD NOT.

IMMEDIATE RESPONSE			SALINE CONTROLS*		AFTER 10 OR MORE TREATMENTS
Case No.	Average time before DPX	One-half hr. after DPX	Average time before saline	One-half hr. after saline	Average clau- dication time
3	94"	2' 11"	1' 56"	1' 14"	No claud. in 5 min.
7	35"	1' 14"	1' 9"	1' 46"	1' 29"
9	1' 5"	1' 42"	1' 10"	2' 11"	3' 54"
13	1' 29"	No claud. in 5 min.	2' 15"	2'	4' 47"
14	44"	47"	1' 2"	1' 17"	No claud. in 5 min.
18	2' 5"	1' 10"	2' 49"	2' 39"	3' 55"
19	2' 13"	No claud. in 5 min.	2' 30"	2' 35"	No claud. in 5 min.
20	1' 46"	No claud. in 5 min.	No claud. in 5 min.	No claud. in 5 min.	No claud. in 5 min.
22	3' 6"	No claud. in 5 min.	1' 12"	1' 45"	No claud. in 5 min.
25	1' 29"	2' 29"	2' 30"	2' 40"	No claud. in 5 min.
28	2' 30"	No claud. in 5 min.	2' 30"	2' 30"	-----
33	51"	1' 35"	49"	50"	-----
36	59"	2' 58"	1' 15"	1' 8"	-----
42	1' 2"	1' 33"	-----	-----	-----

*Most of these tests were made after a week or more of treatment.

DISCUSSION

In reviewing Table IV it should be noted that the previously treated group had already been on a control period of routine therapy, including warm baths, abstinence from tobacco, etc., plus a variety of other measures. This group showed, nevertheless, about the same response after treatment with deproteinated pancreatic extract as the previously untreated groups.

TABLE IV

SUMMARY OF THE RESULTS IN 27 PATIENTS OF TREATING INTERMITTENT CLAUDICATION SECONDARY TO ARTERIOSCLEROTIC PERIPHERAL VASCULAR DISEASE WITH DEPROTEINATED PANCREATIC EXTRACT

CLAUDICATION TIME AVERAGES†

TYPE AND NO. OF CASES	IMMEDIATE RESPONSE		SALINE CONTROLS*		AFTER 10 OR MORE TREATMENTS
	BEFORE	ONE-HALF HR. AFTER	BEFORE	ONE-HALF HR. AFTER	
8 Untreated Uncomplicated	1' 26"	2' 3"†	3' 4"†	2' 52"†	4' 28"† 5 cases 3 cases had less than 10 treat.
5 Untreated complicated	1' 43"	3' 55"†	1' 39"	1' 55"	4' 9"† 4 cases 1 case had less than 10 treat.
14 Previously treated with other therapy Complicated Uncomplicated	1' 32"	2' 54"†	2' †	2' 6"†	4' 24"† 10 cases 4 cases had less than 10 treat.
TOTALS (27)	27 1' 34"	27 3' 1"†	24 2' 15"†	24 2' 18"†	19 4' 19"† 19 cases 8 cases had less than 10 treat.
Extremes	35" to 2' 30"	47" to 5' plus (9)	49" to 5' plus (3)	47" to 5' plus (4)	1' 29" to 5' plus (12)

*Most of these tests were made after a week or more of treatment.

†These averages include cases in which there was no claudication in 5 minutes, and therefore are minimum figures. The true averages would in every case be greater.

Three cubic centimeters of deproteinated pancreatic extract, given intramuscularly on alternate days, appears to be the most satisfactory dose. Larger doses did not, in our experience, seem to produce more beneficial results nor a more prolonged action. Further studies on dosage might be worth while. No untoward reactions have been noted in giving more than 1,000 injections of this substance. It has been

given intravenously to twenty of our patients without severe systemic reactions. We do not advocate its intravenous use at this time, but mention this observation only to emphasize the lack of toxicity. Because of the high protein content of previously used pancreatic extracts, intravenous injections have been definitely associated with risk. The fact that protein is practically absent from this preparation eliminates this danger. Further studies concerning this mode of administration will be reported in the near future.

The mechanism of the action of pancreatic tissue extracts has never been satisfactorily explained, although a hormonal or replacement action similar to that of insulin is the most popular theory today. Assay methods on animals, in which its antagonistic action to adrenalin has been demonstrated, indicate a vasodilatation factor. This effect has not been noted in man. We are at present engaged in studies which may clarify this problem.

The ergometer demonstrated improvement in certain instances in which the patient stated that he had not been benefited. Of 100 patients followed for a period of four to six months while under treatment with deproteinated pancreatic extract, seventy-four reported definite clinical improvement. Many of these were not checked with the ergometer. The other twenty-six failed to show sufficient improvement to warrant continued use of the extract. Spontaneous improvement and regression are common in this condition. It is only by studying a group of patients over a long period of time, and by using a standard method of testing, that conclusions may be drawn as to the value of anything which may be used in the treatment of intermittent claudication due to peripheral arteriosclerosis.

Further refinement and analysis of these extracts may produce fractions that are therapeutically more potent than this one.

SUMMARY

- (1) We have described an apparatus to measure claudication time.
- (2) Following one injection of deproteinated pancreatic extract, twenty-three of a series of twenty-seven patients with arteriosclerosis obliterans showed an improvement (prolongation) of their claudication time. This initial response was in most instances temporary.
- (3) Following ten or more injections of deproteinated pancreatic extract, nineteen patients showed improvement in their claudication time.
- (4) After a series of ten or more treatments, the claudication time was, in this series, prolonged to an average of more than three times that of the control tests.
- (5) Physiologic saline failed to produce an increase in claudication time under identical conditions.
- (6) Further studies will be necessary to determine the extent to which improvement may be advanced, and the duration of the favorable effects after cessation of the treatment.

The authors wish to express their appreciation to Dr. John Miller and Miss Ellen McDevitt for their aid in this study.

REFERENCES

1. Frey, Emil K., and Kraut, Heinrich: Über einen von der Niere ausgeschiedenen, die Herztätigkeit anregenden Stoff. *Zeitschr. f. Physiol. Chem.* 157: 32, 1926.
2. Wolffe, Joseph B.: The Therapy of Tissue Extract, *Tr. Am. Therap. Soc.* 31: 31, 1931.
3. Wolffe, Joseph B., Findlay, Donald, and Dessen, Edward: Treatment of Angina Pectoris With a Tissue Vasodilator Extract—Preliminary Report, *Ann. Int. Med.* 5: 625, 1931.
4. Schwarzmänn, M. S.: Die Behandlung der Claudicatio Intermittens mit Muskel-extract, München. *Med. Wehnschr.* 77: 758, 1930.
5. Elliot, Albert H., and Nuzum, Franklin R.: The Pharmacologic Properties of an Insulin-Free Extract of Pancreas and the Circulatory Hormone of Frey, *J. Pharmacol. and Exper. Therap.* 43: 463, 1931.
6. Barker, Nelson W., Brown, George E., and Roth, Grace M.: Effect of Tissue Extracts on Muscle Pains of Ischemic Origin (Intermittent Claudication), *Am. J. Med. Sci.* 189: 36, 1935.
7. Duryee, A. Wilbur: Tissue Extract in the Treatment of Peripheral Vascular Disease, *Tr. Am. Therap. Soc.* 35: 124, 1935.
8. Hitzrot, L. H., Naide, M., and Landis, E. M.: Intermittent Claudication Studied by a Graphic Method, *AM. HEART J.* 11: 513, 1936.

ACTIVITIES ASSOCIATED WITH THE ONSET OF ACUTE CORONARY ARTERY OCCLUSION

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INTRODUCTION

IN SEVERAL previous reports,¹⁻³ based upon an analysis of 800 attacks of coronary artery occlusion, we presented data in support of the belief that acute coronary artery occlusion is not causally related to physical effort or excitement. These reports also reviewed the literature on this subject. In this paper we offer further evidence, based on study of 1,440 attacks, that coronary artery occlusion occurs irrespective of physical activity.

It is important to distinguish clearly between an attack of angina pectoris and one of coronary artery occlusion. The former is definitely related to exertion, meals, excitement, cold. Although coronary sclerosis is the underlying pathologic condition in both angina pectoris and coronary occlusion, the former is a functional syndrome resulting from transient coronary insufficiency, whereas in coronary occlusion the myocardium is severely injured. In an attack of angina pectoris the patient is usually incapacitated for only a few minutes and is as well after the attack as before. When coronary artery occlusion occurs, however, the patient suffers severe, prolonged pain, may collapse, and develops signs of diminished cardiac output and heart failure. If the attack is survived, physical incapacity persists for weeks or months.

We have also excluded cases of myocardial infarction due to coronary insufficiency. In this condition there is no acute occlusion of a coronary artery, but the coronary circulation is impaired, resulting in necrosis of the heart muscle. It occurs usually with aortic stenosis, surgical operations, tachycardia, acute hemorrhage, pulmonary embolism, and other conditions associated with shock. It is conceivable that, when severe coronary artery disease exists, strenuous effort will produce coronary insufficiency and myocardial infarction without actual coronary occlusion. However, this syndrome differs clinically and electrocardiographically from typical coronary occlusion; the two should not be confused. In coronary insufficiency without occlusion the pain is likely to be less severe and prolonged than in typical coronary occlusion, and in the electrocardiogram there is depression of the R-T segment instead of elevation. Coronary insufficiency is an entity in itself and has been described by many authors.^{4, 5}

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Received for publication May 11, 1939.

MATERIAL

Our data have been derived from a study of 1,440 attacks of coronary artery occlusion observed in 1,077 patients. The latter were almost equally divided between patients seen in the wards of The Mount Sinai Hospital, New York, and those observed in a private consultation practice. We have not included compensation cases because a patient seeking compensation is prone to exaggerate his story and to attribute the attack to some particular event.

Our series includes persons in all walks of life and occupations: factory workers and unskilled and skilled laborers, such as tailors, pressers, peddlers, painters, and printers; store workers; "white-collar" men and office workers; business and professional people, such as merchants, bankers, executives, physicians, teachers, lawyers, and engineers; and housewives (Table I). Of the employed (excluding

TABLE I
OCCUPATIONS IN 1040 CASES OF CORONARY ARTERY OCCLUSION

OCCUPATION	NUMBER	PERCENTAGE
Workers and laborers	377	36.2%
Store workers	55	5.3%
"White-collar" and office workers	90	8.7%
Business men	114	11.0%
Professional men	86	8.3%
Housewives	221	21.2%
None, or retired	96	9.2%

housewives and retired persons) 52 per cent were unskilled and skilled workers, 37 per cent were office workers, store workers, and business men, and the remaining 11 per cent were professional people. This occupational distribution is practically identical with that in the general population of New York City (Table II). Coronary artery occlusion, therefore, is no respecter of poor or rich, laborer or sedentary worker.

TABLE II
COMPARISON OF DISTRIBUTION OF OCCUPATIONS AMONG PATIENTS WITH CORONARY OCCLUSION AND IN GENERAL POPULATION

OCCUPATIONS	CORONARY OCCLUSION	U. S. CENSUS N. Y. C., 1930	JEWISH GAIN- FUL WORKERS
All occupations	722	3,187,459	799,258
Workers and laborers	377 (52%)	1,766,458 (55%)	410,343 (51%)
Store proprietors (retail), "white-collar" and office workers, business men	266 (37%)	1,169,713 (37%)	300,615 (38%)
Professional workers	79 (11%)	251,178 (8%)	88,300 (11%)

We have been able to record the circumstances at the onset of the symptoms of coronary artery occlusion in 930 cases (Tables III and IV). In addition, in 200 cases detailed histories were obtained concerning the patients' activities the whole day before, and even several

TABLE III

ACTIVITIES AT THE ONSET OF CORONARY ARTERY OCCLUSION

ACTUAL ACTIVITY			ASSOCIATED FACTORS				
ACTIVITY	NO.	IN-CIDENCE	MEALS	EXCITEMENT	OPERATION	INFECTION	MISCELLANEOUS
Sleep	198	22.3%	15	2	9	1	
Rest	277	31.1%	15	17	46	24	3, diabetic acidosis 2, trauma 1, typhoid injection
Mild activity	180	20.2%	25	15	6	5	2, smoking 2, insulin injection
Moderate activity	76	8.5%	3	6	2	2	
Walking	141	15.8%	10	3	0	0	
Unusual exertion	18	2.0%	0	0	0	1	
Undetermined	40		24	9	0	7	0
Unknown	510						
Total	1440		92 (9.9%)	52 (5.6%)	63 (6.6%)	40 (4.3%)	10 (1.1%)

weeks before, their attacks. In these a special questionnaire was used (Table V). Incidentally, the frequency and character of premonitory symptoms were thus determined, and these will be subsequently reported.

Table III shows that the attack occurred during sleep in approximately one-fourth of the cases, and during rest in almost one-third. Thus, 53.4 per cent of all the attacks occurred under conditions of rest and sleep, a percentage that corresponds to the fraction of the day spent in rest and sleep. Twenty per cent of the patients were engaged in mild activity at the time of the attack; that is, they were dressing, standing, talking, sitting in the office, etc. Eight and one-half per cent were doing moderately heavy work, such as painting, baking, driving a car, and 2 per cent were engaged in some unusually severe effort, i.e., swimming, skating, playing football, running, carrying a heavy load. We have grouped the patients who were walking, separately; walking preceded approximately 16 per cent of attacks. Thus, 44.5 per cent of attacks were associated with some mild or moderate activity, or with walking, and only 2 per cent with severe exertion.

In addition to the foregoing activities or inactivity, in 257 attacks an associated factor, such as eating, excitement, a surgical operation, infection, or one of several miscellaneous circumstances, was present. In 92 patients (9.9 per cent) the attack of coronary occlusion was associated with eating, i.e., the closure occurred while the patient was eating, or within one or two hours thereafter. In 37 cases the attack followed a heavy meal, and, in the remainder, a light one. Included in this group are 15 patients who suffered the attack in sleep after a heavy meal, and ten who were stricken while walking directly after a meal. A large number of attacks, although related to a meal, occurred during rest or ordinary mild activity.

TABLE IV

TYPES OF ACTIVITY AT ONSET OF CORONARY ARTERY OCCLUSION (930 ATTACKS)

TYPES OF ACTIVITY	NUMBER	PERCENTAGE
A. Primary Activities (890 attacks):	198	22.3%
1. Sleep	277	31.1%
2. Rest—lying down or sitting up	180	20.2%
3. Ordinary mild activity		
62, in home (dressing, standing, walking about, playing with children, talking, retiring, etc.); 35, in store or office; 14, sitting in car or train; 9, in doctor's office or clinic; 8, doing light housework; 6, getting out of bed; 5, taking showers or bath; 5, getting out of bus or car; 5, playing cards; 4, attending a meeting; 4, sitting in a movie; 2, in restaurant; 21, miscellaneous.		
4. Moderate activity (except walking)	76	8.5%
35, working as laborers (painter, engineer, carpenter, baker, tailor, presser, etc.); 16, driving car; 8, during bowel movement or straining at stool; 6, shopping; 2, coughing; 2, running upstairs; 2, during coitus.		
5. Walking	141	15.8%
107, in street; 11, upstairs; 6, after meals; 5, against cold wind; 4, uphill; 4, downstairs; 2, in snowstorm; 2, carrying ten pounds.		
6. Unusual or severe exertion	18	2.0%
9, during or immediately after sport or games (football, swimming, dancing, skating); 5, lifting or moving a heavy load; 3, running for train; 1, after long automobile ride.		
B. Associated Factors (930 attacks):		
1. Meals	92	9.9%
37, heavy meal; 33, ordinary meal; 22, light meal; 15, in sleep; 10, while walking.		
2. Excitement	52	5.6%
13, gambling or playing cards; 8, during argument; 4, at movies; 3, news of deaths of relatives; 3, fright; 3, at wedding or banquet; 2, making speech; 2, during coitus; 1, at funeral; 13, miscellaneous (emotional upset).		
3. Surgical procedures	63	6.6%
26, laparotomy; 20, genitourinary operation; 7, eye, ear, nose or throat operation; 3, leg operation; 2, thyroidectomy; 1, thoracotomy; 1, tooth extraction; 1, incision of furuncle; 1, paravertebral block; 1, bronchoscopy.		
4. Infection	40	4.3%
14, upper respiratory infections; 6, grippe; 4, cholecystitis; 2, peritonitis; 3, pyelonephritis; 4, pneumonia; 2, appendicitis; 2, sepsis; 3, abdominal suppuration.		
5. Miscellaneous	10	1.1%
3, diabetic acidosis; 2, insulin injections; 2, trauma (1 fall on chest and 1 injury to eye); 2, smoking; 1, typhoid injection.		

TABLE V
ONSET OF CORONARY ARTERY OCCLUSION—QUESTIONNAIRE

Name	Adm. No.	Age and Sex	Occ.
Date of onset		Hour of onset	
Description of work:		Type, hours, rest, etc.	
History of angina pectoris, dyspnea, etc., with precipitating factors:			
Activities 4 weeks preceding onset:			
Premonitory symptoms and activities preceding and attending them (dates):			
Onset of symptoms of attack and activities preceding and attending them (dates):			
Summary activity during onset, preceding 24 hours, week, 4 weeks:			
Tobacco		Liquor	
Remarks:			

Fifty-two attacks (5.6 per cent) set in during excitement; that is, while gambling, or during or directly after an argument, or during or after fright, etc. The great majority of these patients were at rest or engaged in ordinary mild activity at the time of the emotional upset.

Sixty-three attacks (6.6 per cent) occurred within three weeks following a surgical operation, and infections of various types preceded the attack in forty cases (4.3 per cent). These included upper respiratory infection, cholecystitis, peritonitis, and pneumonia. Approximately half of these cases are also included in the postoperative group.

A small miscellaneous group comprises three attacks during diabetic coma, two after insulin injections, two while smoking, and one soon after a typhoid vaccine injection. Two attacks were associated with trauma—in one case a fall, and in the other a blow on the eye. In twelve cases the onset of the occlusion was manifested by repeated attacks of angina pectoris of increasing severity, thus making it difficult to determine just when the occlusion occurred. In eight cases the occlusion was silent; there was no history of pain, pressure, or other symptoms.

There was no preponderance of attacks in any particular period of the day (Table VI). Of the 722 attacks in which the time of onset

TABLE VI
TIME OF ONSET OF CORONARY ARTERY OCCLUSION IN 722 ATTACKS

PERIOD OF THE DAY	ATTACKS	INCIDENCE
Morning (7 A.M.-1 P.M.)	209	28.9%
Afternoon (1 P.M.-7 P.M.)	167	23.1%
Total (7 A.M.-7 P.M.)	376	52.0%
Evening 7 P.M.-1 A.M.)	162	22.5%
Night (1 A.M.-7 A.M.)	184	25.5%
Total (7 P.M.-7 A.M.)	346	48.0%

was known, 23.1 per cent occurred in the afternoon (1 P.M. to 7 P.M.), 22.5 per cent in the evening (7 P.M. to 1 A.M.), and 25.5 per cent in the night (1 A.M. to 7 A.M.). A slightly greater number occurred during the morning hours (7 A.M. to 1 P.M., 28.9 per cent). Fifty-two per cent of the attacks began during the daytime, and 48 per cent during the night. The exact hour of day when the attack occurred was ascertained in 471 cases (Table VII). Although the incidence of coronary occlusion was greatest at 2 A.M. and 10 P.M., it seems that no one hour was especially important.

TABLE VII

TIME OF ONSET OF CORONARY ARTERY OCCLUSION IN 471 ATTACKS

HOUR	NO.	HOUR.	NO.
1 A.M.	21	1 P.M.	23
2	37	2	19
3	19	3	17
4	11	4	14
5	15	5	15
6	19	6	20
	122 (25.9%)		108 (22.9%)
7 A.M.	23	7 P.M.	16
8	18	8	15
9	20	9	16
10	19	10	30
11	23	11	25
12	18	12	18
	121 (25.7%)		120 (25.5%)

DISCUSSION

In reviewing the data on the activities at the onset of the occlusion it will be seen that 53.4 per cent of the attacks occurred during rest and sleep. This association is fortuitous, since one spends about half the day in these states. The same conclusion holds true for physical activity, including mild and moderate exertion and walking, which attended 44.5 per cent of the attacks, since at least two-fifths of the day is spent in such pursuits. Hence the onset of the attack did not depend on the state of physical activity or inactivity of the body. The findings were similar in the 200 cases in which a detailed history was obtained of the patients' activities for days, and even weeks, prior to their attacks.

The factor of unusual or severe exertion must be discussed in some detail. Twenty-five compensation cases which came under the observation of the senior author in private practice were omitted from our series because in such cases the patient's story is likely to be colored and exaggerated. These patients usually attribute their attacks to lifting or moving a heavy load. With the omission of this group, barely 2 per cent of all of the attacks were associated with some unusual effort, such as lifting a heavy load, playing football, swimming,

dancing, running for a train, etc. It may be argued that, although 2 per cent is a small number, the severe effort was a factor in precipitating the coronary occlusion in this small group. However, even the most sedentary person frequently performs some unusual effort during the day; nearly everyone has occasion to run, climb stairs, rush for a bus or train, tug at a drawer, lift a stuck window, park a car, remove a tire from a car, carry a heavy bag or weight, move a piece of heavy furniture, dance, or play golf. Were effort a factor, every day thousands of men and women over the age of 45 or 50 years with coronary artery disease would sustain attacks associated with severe exertion, and the percentage in our series would be much greater than 2 per cent.

It is important to point out that in 60 cases the attack occurred when the patient had been in bed for weeks or months with a chronic illness or a previous coronary occlusion. In these cases there can be no question of effort at any time preceding the attack.

Premonitory complaints, such as pain or pressure in the chest, shortness of breath, and weakness, were noted in 80 of 170 cases in which the history was adequate. These premonitory symptoms appeared several hours or days before the actual attack, during rest or some ordinary activity. As far as we could ascertain, they were not related causally to severe exertion.

Two other groups of data make the conclusion inescapable that activity is of no importance in the precipitation of coronary occlusion. Thus, the period of day and the actual hour when the occlusion occurred played no role, since the number of attacks in the working or play hours did not exceed those in the evening or night hours. In fact, 10 P.M. and 2 A.M. were the peak hours, and certainly the majority of people are resting or sleeping at these times.

The occupational distribution in our cases was practically the same as that in the general population of New York City. Although in one authoritative report⁶ the author maintained that there is a higher incidence of coronary occlusion in the upper strata of society, most figures, including ours, demonstrate that coronary arteriosclerosis affects all classes equally.

It is obvious that when acute myocardial infarction has already occurred, effort may produce pain. It is even possible that strenuous effort may induce pain during the formation of the occluding thrombus, a process which occurs over an interval, and thus make the patient aware of the condition. However, the effort does not play a role in the actual pathogenesis of the occlusion. Trauma, too, may seriously damage the heart and aorta, but it may be repeated that in this paper we are concerned only with the cause of classical coronary artery occlusion.

In recent years, pathologists⁷⁻¹⁰ have emphasized the fact that the thrombus in a coronary artery often results from an intimal hemorrhage into an atherosclerotic plaque. This has been used as corroborative evidence by those (e.g., Paterson¹¹) who maintain that effort and excitement may lead to coronary artery occlusion; they assume that the transitory rise of blood pressure which accompanies the exertion or excitement may cause intimal hemorrhage. Such an assumption is refuted by several observations. Capillary, and even intimal, hemorrhages occur in shock, in which the blood pressure drops to very low levels. Furthermore, Winternitz, et al.,⁹ injected dye into sclerotic coronary arteries at pressures varying from 500 to 1000 mm. Hg without producing rupture of the intimal capillaries. Surely the pressure in the coronary arteries and capillaries during life is very much lower than this, so that hypertension cannot be a factor in intimal hemorrhage.

Whatever the actual pathogenesis of coronary artery occlusion may be, our clinical data appear to us to exclude exertion as a factor. Furthermore, there is no evidence that intimal hemorrhage into a plaque is precipitated by effort: it is part of a degenerative process resulting from pre-existent and progressive atherosclerosis.¹² It appears at the site of the most advanced arteriosclerosis and is probably unrelated to external influences. In fact, intimal hemorrhage was just as frequent a post-mortem finding in our patients who had been confined to bed for weeks as in those who were active before the coronary occlusion.

It is important to consider the relationship of coronary occlusion to meals, which have been assumed to be a precipitating factor. About 10 per cent of the attacks in our series set in during or after a meal; this includes attacks which occurred as long as two hours after a meal, providing it was a heavy one. Considered in this way, the period of day in relation to the three meals is much more than 10 per cent; hence, one must conclude that in our series the relationship of attacks to meals was fortuitous.

Only 5.6 per cent of the attacks of coronary occlusion in our series showed some association with emotion, in spite of the fact that all of us repeatedly experience some degree of excitement, whether it is a fright, an argument, or a death in the family. Were emotion and excitement factors, one should find them very commonly associated with attacks of coronary occlusion; indeed, it might be dangerous for people over fifty to read a newspaper or listen to the radio.

One cannot rule out infection as a factor in our cases of coronary artery occlusion. It was a frequent complication, particularly in the postoperative cases. Among the patients who had not been operated on, there were 23 instances in which an upper respiratory infection,

grippe, or other acute disease, was present for several days preceding the attack. It will be necessary to gather data from a larger series of cases before a definite conclusion on this point can be reached. The relation of surgery to coronary artery occlusion has been discussed in a previous publication.¹³

SUMMARY

1. One thousand four hundred and forty attacks of coronary artery occlusion were analyzed from the standpoint of the patients' activities preceding the attacks, the time of day when the attacks occurred, the patients' occupations, and other associated factors.

2. The distribution of occupations in this series of cases was approximately the same as that in the general population; therefore, occupation and social status did not predispose to coronary occlusion.

3. The circumstances preceding the onset of symptoms in 890 cases were: sleep, 22.3 per cent, rest, 31.1 per cent, mild activity, 20.2 per cent, moderate activity, 8.5 per cent, walking, 15.8 per cent, and unusual exertion, 2.0 per cent.

4. Correlation of these percentages with the number of hours spent daily by the ordinary person in the same occupations indicated that the circumstances were coincidental and that none of them was causally related to the coronary occlusion. Coronary occlusion occurs irrespective of the state of physical activity of the body.

5. Associated factors in 930 cases were: meals, 9.9 per cent, emotional excitement, 5.6 per cent, surgical operation, 6.6 per cent, infection, 4.3 per cent, and miscellaneous factors, 1 per cent. It was concluded that, with the possible exception of surgical procedures, these factors did not play a role in the pathogenesis of coronary occlusion. Only two attacks of coronary occlusion were associated with trauma.

6. Detailed histories of the activities and emotional state of patients for hours, days, and weeks preceding attacks confirm the belief that physical activity and excitement are not factors in the onset of coronary occlusion.

7. Sixty patients sustained an attack of coronary occlusion after having been bedridden for weeks or months because of some chronic illness.

8. The time of onset of the attack was ascertained in 722 cases. Equal numbers occurred during the afternoon, evening, and night, and a slightly greater number during the morning. The attacks were well distributed throughout all the hours of the day, with peaks at 2 A.M. and 10 P.M. This also indicates that activity is not a factor in the precipitation of coronary occlusion.

9. Premonitory symptoms of the attack, such as chest pain, dyspnea, or weakness, were present in 80 of 170 cases in which these symptoms were investigated.

10. There is no evidence that physical effort or excitement produces intimal hemorrhage in the coronary arteries, which is the usual forerunner of thrombosis and occlusion. Intimal hemorrhage is the end result of the progressive, degenerative arteriosclerotic process and is probably a fortuitous event. It was found at necropsy as frequently in patients who had been bedridden prior to the occlusion as in those who were physically active.

REFERENCES

1. Master, A. M., Dack, S., and Jaffe, H. L.: Factors and Events Associated with the Onset of Coronary Artery Thrombosis, *J. A. M. A.* 109: 546, 1937.
2. Master, A. M., Dack, S., and Jaffe, H. L.: The Relation of Various Factors to the Onset of Coronary Artery Thrombosis, *J. Mt. Sinai Hosp.* 3: 224, 1937.
3. Master, A. M.: Coronary Artery Thrombosis; The Role of Effort, Trauma, and Other Factors in Its Precipitation, *Indust. Med.* 6: 307, 1937.
4. Büchner, F.: Die Zeichen der Herzmuskelschädigung durch Koronarin-suffizienz im histologischen Bild und im Elektrokardiogramm, *Zentralbl. f. inn. Med.* 58: 497, 1937.
5. Levy, R. L., and Bruenn, H. G.: Acute Fatal Coronary Insufficiency, *J. A. M. A.* 106: 1080, 1936.
6. White, P. D.: Climate, Mode of Life and Heart Disease, *Ann. Int. Med.* 12: 6, 1938.
7. Paterson, J. C.: Vascularization and Hemorrhage of Intima of Arteriosclerotic Coronary Arteries, *Arch. Path.* 22: 313, 1936.
8. Paterson, J. C.: Capillary Rupture with Intimal Hemorrhage as a Causative Factor in Coronary Thrombosis, *Arch. Path.* 25: 474, 1938.
9. Winternitz, M. C., Thomas, R. M., and LeCompte, P. M.: *The Biology of Arteriosclerosis*, Springfield, Ill., 1938, Charles C. Thomas.
10. Wartman, W. B.: Occlusion of Coronary Arteries by Hemorrhage Into Their Walls, *AM. HEART J.* 15: 459, 1938.
11. Paterson, J. C.: Relation of Physical Exertion and Emotion to Precipitation of Coronary Thrombi, *J. A. M. A.* 112: 895, 1939.
12. Leary, T.: Vascularization of Atherosclerotic Lesions, *AM. HEART J.* 16: 549, 1938.
13. Master, A. M., Dack, S., and Jaffe, H. L.: Postoperative Coronary Artery Occlusion, *J. A. M. A.* 110: 1415, 1938.

CONVALLAN IN CARDIAC THERAPY

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CONVALLARIA MAJALIS, or lily-of-the-valley, has been known for many years as a cardiac tonic and diuretic. However, convallaria has played a very small role in the therapy of cardiac disease because the preparations available have not been standardized and are often inert.

Until recently the preparations used were mainly infusions and fluid-extracts of leaves, roots, or of the whole plant. Marvin and White,¹ in 1921, showed that the activity of convallaria is due to certain glucosides which resemble digitalis. W. Karrer,² in 1929, isolated a crystalline glucoside of convallaria by extraction with chloroform and named it convallatoxin. An assay of this substance showed that it contained three million frog doses* per gram. Straub,³ in 1937, described an extract prepared by treating an aqueous solution of convallaria with colloidal iron hydroxide and concentrating the filtrate to a powder. This extract he named "convallan." Straub's convallan was found to consist of 20 per cent convallatoxin and 80 per cent "convallamarin complex." Physiologic assays showed that convallan contained 4000 to 8000 frog doses per gram.

Von Bergmann⁴ studied the pharmacologic properties of convallan and found that its activity, as measured in frog doses, showed that it stood between digitalin and strophanthin in therapeutic effect, but was much less toxic than either.

The findings of Von Bergmann were confirmed by Büttner,⁵ who found from his clinical studies that the minimum effective dose was 3000 frog units, that the maximum dose which could be employed was 20,000 units, and that doses of 12,000 frog units may be administered daily with safety. Büttner also found that convallan had little, if any, cumulative action, and that it may be given before or after digitalization with complete safety. Büttner also noted that the pharmacologic action of convallan in large doses was essentially the same as that of digitalis and strophanthin. However, small doses produced a remarkable diuretic effect without causing heart block or increasing the degree of an already existing block.

This interesting observation suggested its use in patients suffering from cardiac failure associated with varying degrees of heart block.

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Received for publication May 14, 1939.

*One frog dose is the smallest amount of a drug, per gram of animal, which will kill a frog when injected into the ventral lymph sac.

The dosage employed in this group of cases was largely empirical and was determined by the pharmacologic effect obtained in the individual patients.

REPORT OF CASES

CASE 1.—B. W., a colored man, aged 82 years, was admitted to the hospital July 13, 1938. The patient, on admission, had evidence of arteriosclerotic heart disease, with severe dyspnea, orthopnea, ascites, bilateral hydrothorax, and marked edema of the ankles and feet. On admission, the electrocardiogram (Fig. 1) showed left bundle branch block. The patient received 2000 F. D.* of convallan daily for four

Fig. 1.

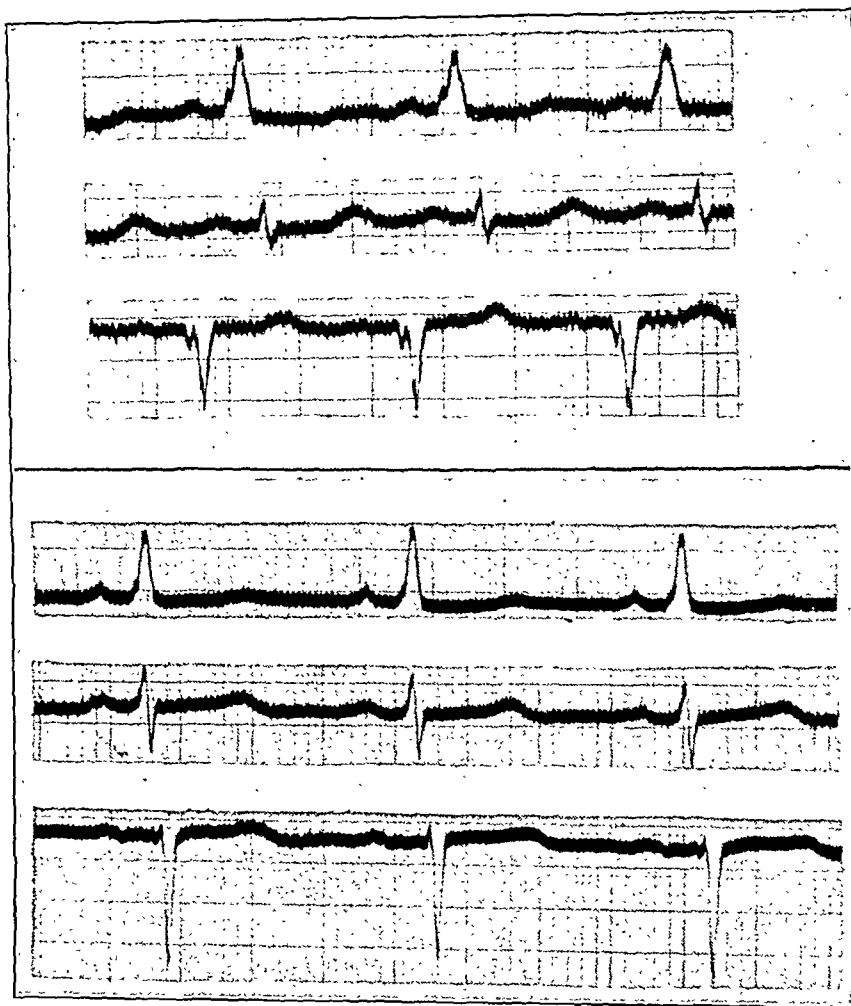


Fig. 2.

Fig. 1.—Case 1, taken on admission into the hospital, showing intraventricular conduction impairment.

Fig. 2.—Case 1, taken nineteen days after the admission electrocardiogram (Fig. 1). Note improvement in intraventricular conduction, slower rate, and repolarization.

days. The dose was then increased to 3000 F. D. for three days, after which he was placed on a maintenance dose of 2000 F. D. daily. There were a rapid loss of anasarca, disappearance of dyspnea, and slowing of the pulse rate. The patient was

*F.D., frog dose,

Fig. 3.

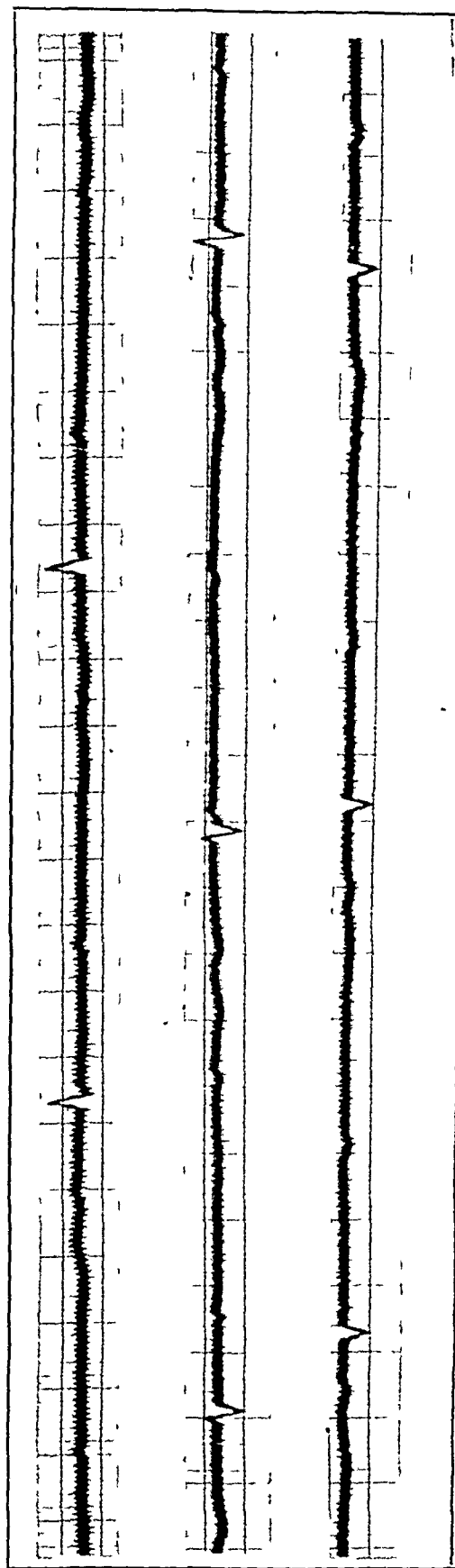


Fig. 4.

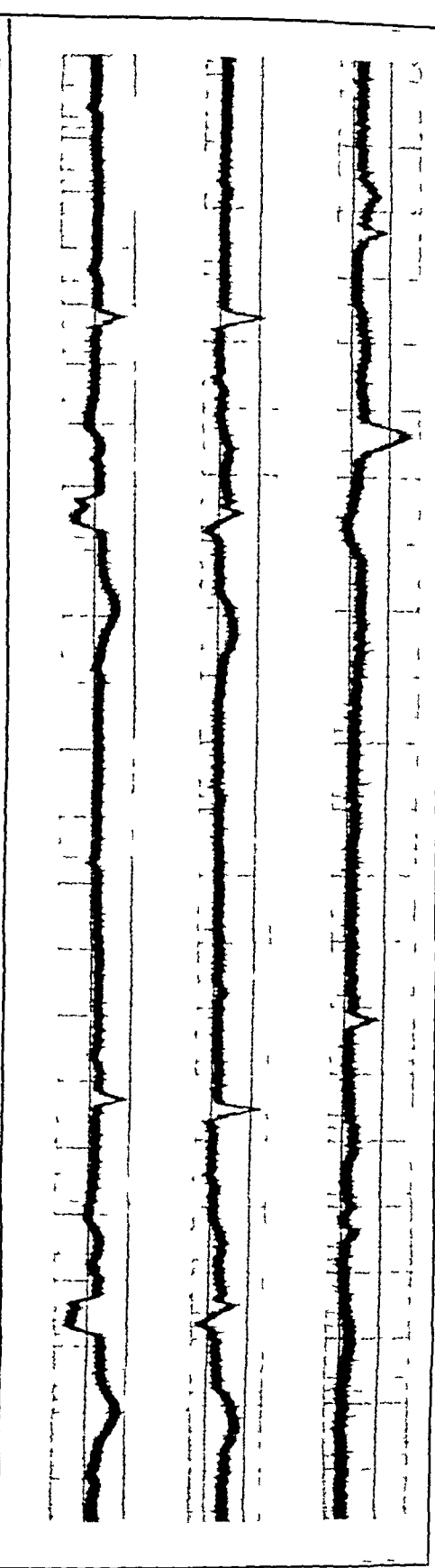


FIG. 3.—Case 2, taken on admission into the hospital, showing complete heart block and bigeminy.
FIG. 4.—Case 2, taken six days after electrocardiogram in FIG. 3. Note absence of bigeminy and more rapid ventricular rate

dismissed nineteen days after admission entirely free from edema. An electrocardiogram (Fig. 2) taken Aug. 1, 1938, showed improvement in the auriculo-ventricular conduction. Ten months after dismissal from the hospital the patient continues in fair condition, having slight edema only occasionally.

CASE 2.—J. R., a white man, aged 79 years, with arteriosclerotic heart disease, was admitted to the hospital Dec. 8, 1938, showing ascites, bilateral hydrothorax, and edema of the legs. On admission, the electrocardiogram (Fig. 3) showed complete A-V dissociation with bigeminy. The patient received 3000 F. D. of convallan daily, and the edema and dyspnea disappeared rapidly. The electrocardiogram (Fig. 4) which was taken Dec. 14, 1938, showed complete A-V dissociation with an auricular-ventricular rate ratio of 2:1, and there was none of the previous bigeminy. The patient was dismissed from the hospital on a maintenance dose of 3000 F. D. daily, and four months later he was still free of edema.

Fig. 5.

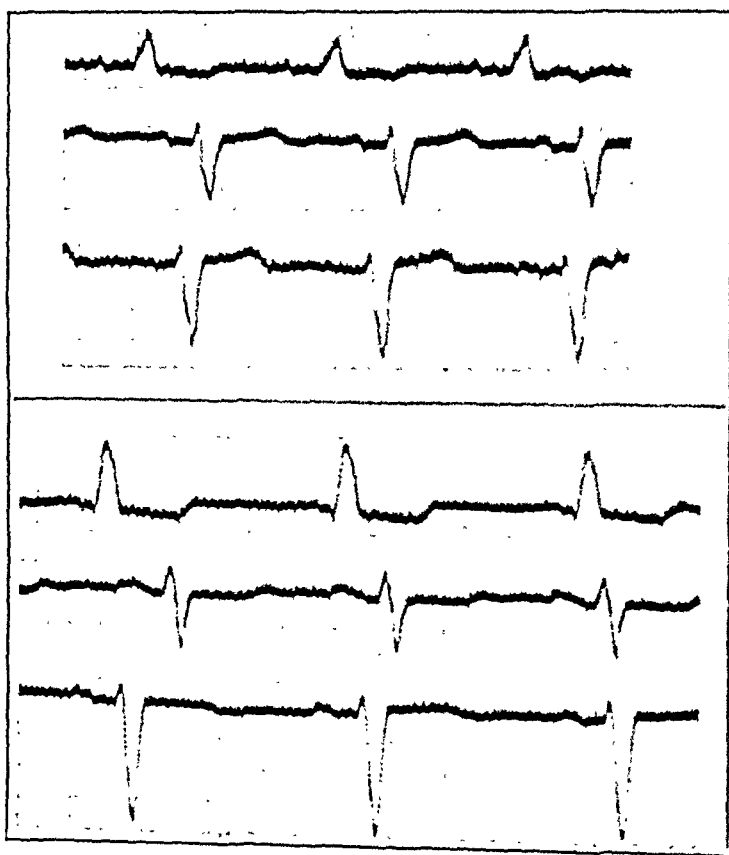


Fig. 6.

Fig. 5.—Case 2, taken before convallan therapy.

Fig. 6.—Case 2, taken after three months of 3,000 F.D. of convallan daily.

CASE 3.—P. L., a white woman, aged 60 years, suffering from arterio-sclerotic heart disease, was admitted to the hospital May 31, 1938. At the time of admission she showed marked dyspnea, anasarca, and edema of the extremities. The patient received digitalis from June 2, 1938, to Jan. 6, 1939, with no noticeable improvement. She then received convallan in doses of 2000 F. D. daily, and in eighteen days she lost 23½ pounds and showed remarkable improvement. The electrocardiogram

(Fig. 5), taken seven days after admission to the hospital, after she had received digitalis, showed no change from previous electrocardiograms; bundle branch block was present. An electrocardiogram taken after three months of convallan therapy (Fig. 6) showed no increase in the degree of heart block, and the patient's condition was much improved.

CASE 4.—P. H., a white man, aged 74 years, was admitted to the hospital Dec. 28, 1938, showing marked dyspnea, gallop rhythm, and edema of the ankles. The patient was found to be suffering from hypertensive cardiovascular disease with cardiac failure. The electrocardiogram (Fig. 7), taken Dec. 29, 1938, showed prolongation

Fig. 7.

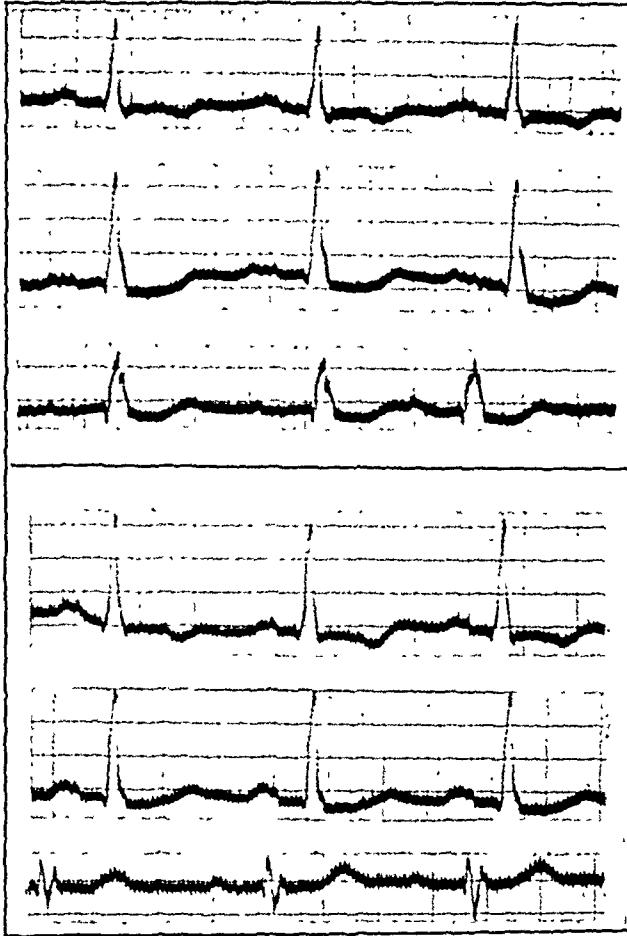


Fig. 8.

Fig. 7.—Case 4, taken on admission to hospital. No axis deviation.

Fig. 8.—Case 4, taken thirty days after admission. Left axis deviation; change in T_1 , T_2 , and T_3 .

of conduction time and some depression of the S-T segments in Leads II and III. He received 3000 F. D. of convallan daily, was promptly relieved of edema and dyspnea, and the gallop rhythm disappeared. The blood pressure, however, remained unchanged. An electrocardiogram (Fig. 8) taken Jan. 30, 1939, showed little change in the heart rate but distinct improvement in auriculoventricular conduction and beginning left axis deviation. This patient was placed on a maintenance dose of 3000 F. D. daily, and four months later he showed continued improvement.

CASE 5.—G. P., a white woman, aged 47 years, a sufferer from hypertensive cardiovascular disease for several years, was admitted to the hospital Jan. 14, 1938, complaining of nausea and vomiting. She showed marked orthopnea and dyspnea. The electrocardiogram (Fig. 9), made Jan. 15, 1938, showed left bundle branch block. The patient was digitalized, but her condition did not improve; after bed rest for nine weeks, the pulse rate remained between 110 and 130, and marked dyspnea was still present. She was then given 3000 F.D. of convallan daily for four days and showed very marked symptomatic improvement. She was dismissed on a maintenance dose of 2000 F. D. daily. The electrocardiogram (Fig. 10) taken April 7, 1938, showed left axis deviation, which was not present in the first electrocardiogram.

Fig. 9.

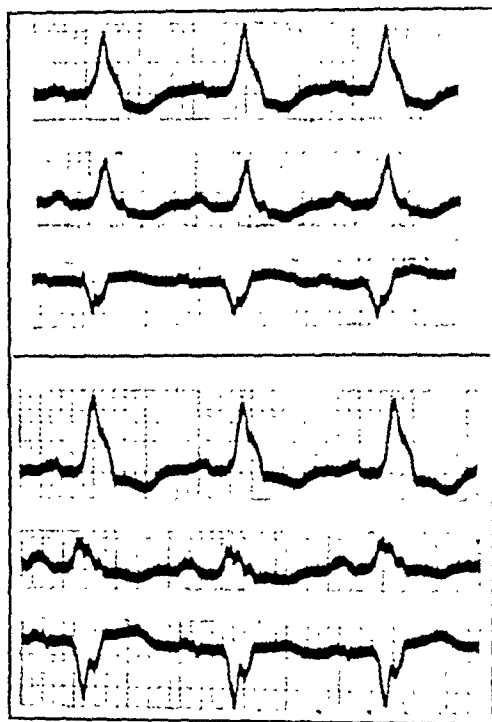


Fig. 10.

Fig. 9.—Case 5, on admission to the hospital. Left bundle branch block. No axis deviation.

Fig. 10.—Case 5, three and one-half months later. Left axis deviation.

This group of cases is a selection from a much larger number in which convallan was used in treatment. In a number of cases of valvular heart disease with marked decompensation, favorable clinical results were obtained, but results no better, and often not as good as those gained by using digitalis. Two patients with lipoid nephrosis were treated with convallan; one responded with complete disappearance of the edema, while the other was unaffected by the drug.

Our impression, after a two-year experience with convallan, is that it can be employed, often with much benefit, in cases of heart block or bundle branch block with cardiac failure in which the administra-

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1. The first step in the process is to identify the problem or goal. This involves understanding the current situation and determining what needs to be achieved. It is important to be clear and specific about the objectives.

2. Once the problem is identified, the next step is to gather information. This can be done through research, consultation with experts, or by collecting data. It is essential to have a thorough understanding of the problem before attempting to solve it.

3. After gathering information, the next step is to develop a plan. This involves identifying the steps that need to be taken to achieve the goal. The plan should be realistic and achievable, and it should take into account any potential obstacles or challenges.

4. Once a plan is developed, the next step is to implement it. This involves putting the plan into action and monitoring progress. It is important to stay focused and committed to the plan, and to be prepared to make adjustments if necessary.

5. The final step in the process is to evaluate the results. This involves assessing the outcomes of the plan and determining whether the goal has been achieved. It is important to reflect on the process and learn from any mistakes or challenges that were encountered.

CAPILLARY RUPTURE WITH INTIMAL HEMORRHAGE AS A CAUSE OF PULMONARY THROMBOSIS

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THE differentiation between primary thrombosis of the pulmonary artery and embolism due to the transport of thrombus material from a distant site is difficult. When the occluding masses occupy the entire arterial lumen, as they usually do, one is forced to consider them as emboli, even when the site of primary thrombosis cannot be found. However, small mural thrombi which occupy only a part of the lumen and are firmly attached to the arterial wall can be regarded as primary depositions. Two such cases of thrombosis, *in situ*, of the pulmonary artery and its branches are reported here. It was interesting to note that the mechanism of thrombus deposition in each case appeared identical with that which I have described in sclerotic coronary arteries,¹ namely, capillary rupture with intimal hemorrhage into an atherosclerotic plaque.

CASE REPORTS

CASE 1.—A 64-year-old woman was admitted to hospital four months before death, complaining of weakness in both legs, pain in the back, and debility. Examination revealed a severe hypochromic anemia, marked kyphosis of the lower dorsal vertebrae, and paraplegia. She grew worse steadily, and developed signs of bronchopneumonia as a terminal feature. Decubitus ulcers were present.

Autopsy revealed almost complete destruction of the tenth, eleventh, and twelfth thoracic vertebrae by a tuberculous process, with secondary infection by Gram-negative bacilli. The spinal cord at the level of the eleventh thoracic vertebra was compressed and thinned out to approximately one-third its normal width. Acute, bilateral bronchopneumonia was the immediate cause of death. Additional autopsy findings were leiomyoma of the uterus, bilateral cortical adenomata of the adrenal glands, old pleural adhesions, and severe hypochromic anemia.

The apex of the left ventricle contained a firmly adherent mural thrombus, the center of which was liquefied and showed Gram-negative bacilli on direct smear. No infarction, old or recent, was noted in the adjacent myocardium. The aorta, coronary arteries, and the pulmonary artery and its main branches showed a moderate grade of atherosclerosis. In the pulmonary artery there were numbers of small, slightly raised, yellowish flecks, the process extending down as far as the tertiary branches. In one of the latter, on the right side, a pedunculated mass of thrombus was attached firmly to the apex of an elevated plaque. This thrombus measured approximately 6 by 2 by 2 cm.; it was pear-shaped, and its pedicle was quite narrow. The thrombus occupied about one-fourth of the lumen of the artery. The entire thrombus and the adjacent part of the arterial wall were embedded in paraffin in one block, and sectioned serially at intervals of 100 μ , the sections being cut longitudinally. The sections were stained with hematoxylin and eosin and with Perle's stain for iron pigment.

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Received for publication May 29, 1939.

Microscopically, the intima of the artery showed a diffuse thickening of the fibrous "endarteritic" variety, but at the point of thrombus attachment there was an atheromatous plaque into which hemorrhage had occurred. The hemorrhage appeared to vary in age in different parts of the atheromatous plaque; the central portion showed intact red cells, while at the periphery hemosiderin could be demonstrated with Perle's stain. The intervening space was occupied

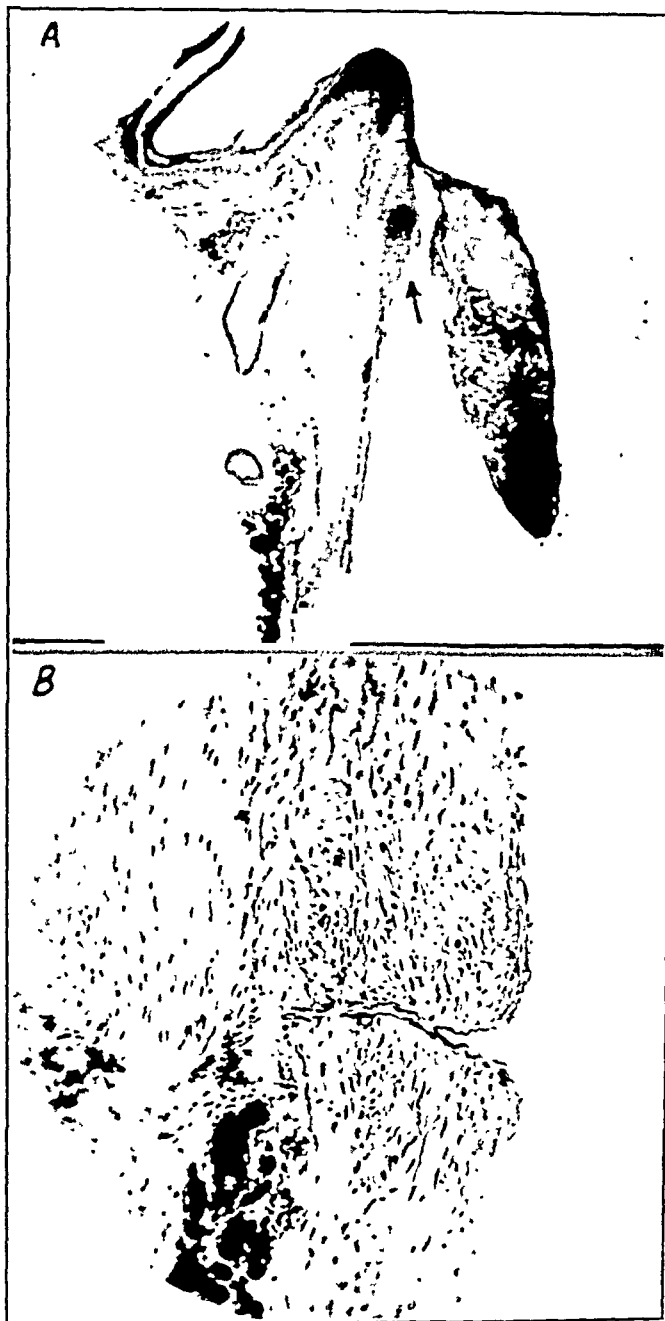


Fig. 1.—A, a longitudinal section through a branch of the pulmonary artery in Case 1. A pedunculated thrombus projects into the lumen and is attached to the arterial wall at a point (shown by the arrow) where hemorrhage had occurred into an atherosclerotic plaque. The thrombus was partially separated at this point during the process of sectioning. Hematoxylin and eosin stain was used. $\times 18$.
B, a section through the same branch artery, showing a small capillary arising from the lumen and penetrating the intima. Hematoxylin and eosin stain was used. $\times 130$.

by homogeneous material which stained pink with eosin and resembled "fibrinoid" material. The pedicle of the thrombus was attached to the apex of the hemorrhagic focus, and here it showed advanced organization and hemosiderin production (Fig. 1*A*). The body and tip of the thrombus were of more recent origin, consisting of skeins of fibrin and platelets with enmeshed red cells and leucocytes. No intimal capillaries could be made out in the area of intimal hemorrhage, but farther down in the artery a small capillary was noted, arising from the lumen and penetrating the thickened intima (Fig. 1*B*).

CASE 2.—An 81-year-old man was admitted to hospital five weeks before death, complaining of frequency of micturition of six years' duration, and of a painful swelling in the perineum for one month. On examination, the prostate gland was found to be symmetrically enlarged, firm, and smooth. There was a painful, indurated swelling in the perineum which displaced the scrotum forward, and extended from the left inguinal region to within half an inch of the anus. Two days after admission this swelling was incised, and a large amount of purulent material evacuated. Cultures of this material grew a nonhemolytic streptococcus, *Staphylococcus aureus*, and *B. coli*. Two weeks later cystostomy was performed. Subsequently he grew worse. A spreading ulcer developed at the point where the perineal abscess had been drained. At no time in the postoperative period were there any signs or symptoms referable to the lungs.



Fig. 2.—A slightly enlarged photograph of a tertiary branch of the pulmonary artery in Case 2. Most of the intimal hemorrhages are situated about the orifices of branch arteries. The endothelium over some of the hemorrhages is intact, while over others it is ulcerated and replaced by mural thrombus.

Autopsy revealed an adenomyoma of the prostate gland, acute necrotic cystitis, acute and chronic osteomyelitis of the pubic bone, brown atrophy of the heart, and a moderate grade of cerebral edema.

The right common iliac vein and the right external iliac vein were completely occluded by an adherent mass of thrombus. The pulmonary artery and its main branches showed numerous, slightly raised, yellowish, atherosclerotic plaques. In addition, the intimal surface of many of the secondary, tertiary, and smaller branches of the pulmonary artery showed numbers of greyish-brown, irregularly

rounded swellings, most of which were situated close to the orifices of branch arteries (Fig. 2). They varied between 1 mm. and 1 cm. in diameter. The endothelial surface over some of the swellings was intact; over others it was ragged and apparently ulcerated, while over a few thrombus was attached to it. One branch artery was almost completely occluded by thrombus. Six of these lesions

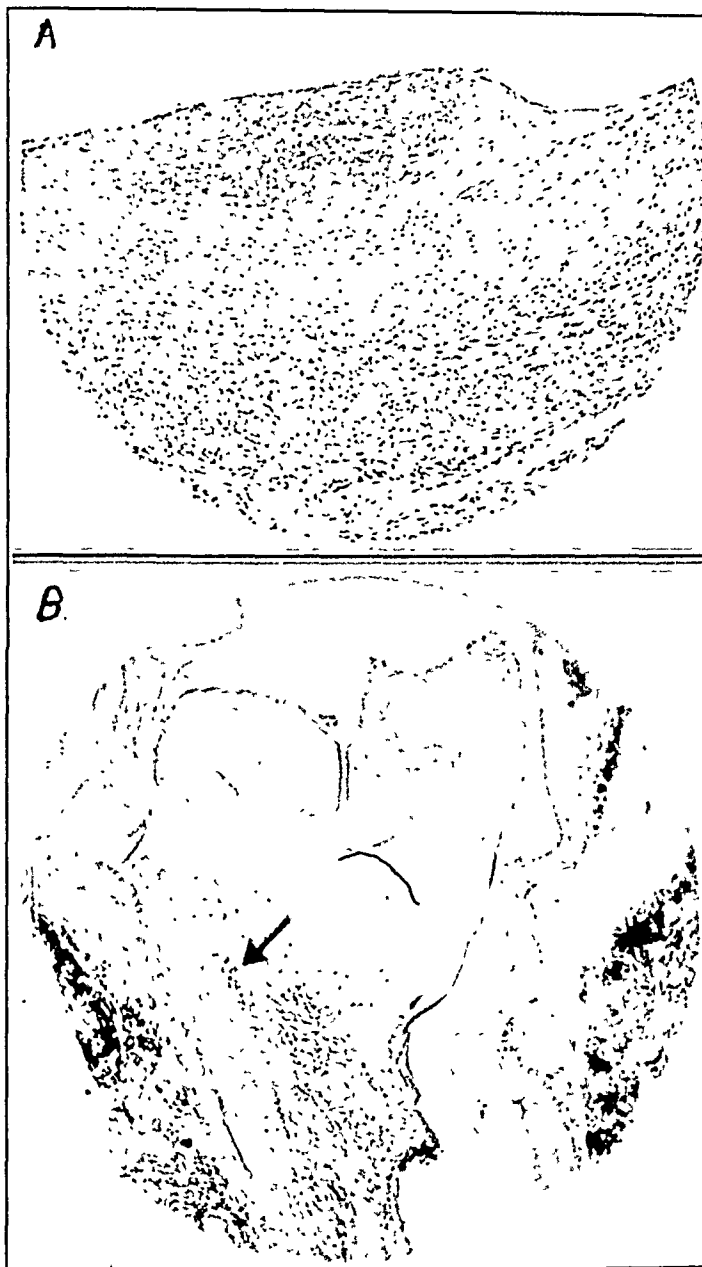


Fig. 3.—A, a section of one of the intimal hemorrhages in Case 2. The endothelium and the superficial intimal layers are intact and are elevated by the hemorrhage. Hematoxylin and eosin stain was used. $\times 55$.

B, a longitudinal section through a small branch artery in Case 2. The lumen is almost occluded by a thrombus which is attached at a point (marked by the arrow) where hemorrhage had occurred into an atherosclerotic plaque. Hematoxylin and eosin stain was used. $\times 20$.

were embedded in paraffin and sectioned serially at intervals of 100 μ . The sections were stained with hematoxylin and eosin. Three others were sectioned by freezing, and the sections were stained with Sudan III and hematoxylin.

Microscopically, each of the areas of intimal discoloration was found to represent a hemorrhage into the subendothelial tissues. Intact red cells could be seen in most of the hemorrhages; organizing blood clot was present in some; and occasionally hemosiderin could be demonstrated, particularly at the outer edge of the hematoma. Small capillaries lying in proximity to the extravasated blood and to the lumen of the artery were seen in several of the sections. The endothelium and the subendothelial tissues overlying the hemorrhages were intact in a few instances (Fig. 3*A*), and in these there was no evidence of thrombosis. However, in the majority the superficial layers could not be made out, the area of hemorrhage gradually merging into a ragged mass of thrombus which projected slightly into the lumen of the artery. In one instance the lumen of a branch artery was almost completely occluded by a large thrombus which was attached to the apex of a small atherosclerotic plaque into which hemorrhage had occurred (Fig. 3*B*). The frozen sections which were stained with Sudan III and hematoxylin showed stainable fat intermingled with blood in most of the intimal hemorrhages.

COMMENT

Because most of the pulmonary thrombi in these two cases occupied only a small part of the arterial lumen, and because they were firmly attached to the intima by organizing tissue, one can safely assume that they were formed *in situ*. The principal causes of pulmonary thrombosis, as given in the literature, are stasis of blood in aneurysmal sacs, inflammatory lesions of the arterial wall (either primary arteritis or secondary arteritis due to the spread of inflammation from the adjacent lung tissue), and atherosclerosis with the formation of atheromatous "ulcers." Less commonly, other conditions may act as contributory causes—increase in the blood calcium, polycythemia, dehydration and anoxemia, and myocardial insufficiency with consequent slowing of the pulmonary circulation. From the findings in the two cases reported here, it would appear that capillary rupture with hemorrhage into atherosclerotic plaques should be included in the list of principal causes.

The intimal hemorrhages in these two cases were similar in structure to those previously described in sclerotic coronary arteries and in association with coronary thrombi.¹ They had occurred into atheromatous foci, and in several instances small capillaries which arose from the arterial lumen lay in proximity to the extravasated blood. It is admitted that intimal hemorrhages of the coronary arteries result from the rupture of intimal capillaries.^{1, 2, 3} Intimal hemorrhages in the pulmonary artery and its branches can be considered to be of similar origin. Furthermore, because the intimal hemorrhages were found at the point of attachment of all the pulmonary thrombi in the two cases, it would appear that the liberation of thromboplastic substances, either from the hemorrhages proper, or from other lesions which are secondary to capillary rupture, was responsible for thrombosis.

I have already suggested that the main causes of capillary dilatation and rupture in sclerotic coronary arteries, in the order of their importance, are (1) high intracapillary blood pressure due to persistent or

transient hypertension, (2) softening by atheroma of the stroma supporting the capillary wall, and (3) increased capillary fragility. There is reason to believe that this order of causative factors should be reversed in cases of pulmonary thrombosis.

The normal systolic blood pressure in the pulmonary artery is said to be 30 to 40 mm. Hg, a pressure which is low compared to that in the aorta and its main branches; and there were no findings in the two cases reported here to suggest that the intrapulmonary pressure had been abnormally raised for any length of time. That is to say, there were in neither case any pathologic lesions such as mitral stenosis, brown induration of the lungs, hypertrophy of the right ventricle, or chronic passive congestion of the liver and spleen, all or some of which are usually associated with long-standing high pressure in the lesser circulation. Except for the possibility of a sudden and transient increase in the intrapulmonary pressure in these two cases, a highly improbable condition, the factor of increased intracapillary pressure in the production of dilatation and rupture of intimal capillaries in the pulmonary artery appears to be of little importance.

The influence of atheromatous degeneration in the production of intimal hemorrhages in the pulmonary circulation is difficult to estimate. Softening is a physical character of atheroma, and it is assumed that the softening process allows the wall of a capillary to dilate and rupture as the result of the pressure within its lumen. While both gross and microscopic evidence of atherosclerosis was present in the pulmonary artery in each of the cases reported here, the lipoid deposits were not nearly so massive as those affected by intimal hemorrhage in the coronary arteries. Indeed, most of the hemorrhages in Case 2 had occurred into the more superficial subendothelial tissues. It would appear, therefore, that the rupture of the intimal capillaries in these two cases cannot be laid to overdilatation from increased intracapillary pressure or from excessive atheromatous degeneration. Inasmuch as other information was lacking, it was probably due to increased capillary fragility. It is known that the walls of capillaries become more fragile with advancing age;⁴ one of the patients was 81 years old, and the other, while only 64, appeared prematurely aged, presumably as the result of a long-standing tuberculous infection. Other factors that may affect the fragility of intimal capillaries in general are now being investigated.

SUMMARY AND CONCLUSIONS

Two cases of thrombosis of the pulmonary artery and its branches are reported. In each case the various thrombi were attached to the intima at points where hemorrhages into atheromatous plaques had occurred. It would appear that intimal hemorrhage in the pulmonary artery results from the rupture of capillaries which are derived from

the arterial lumen. The rupture of intimal capillaries with intimal hemorrhage should be included in the list of causes of pulmonary artery thrombosis.

REFERENCES

1. Paterson, J. C.: Vascularization and Haemorrhage of the Intima of Arteriosclerotic Coronary Arteries, *Arch. Path.* **22**: 313, 1936.
Capillary Rupture With Intimal Haemorrhage as a Causative Factor in Coronary Thrombosis, *Arch. Path.* **25**: 474, 1938.
Relation of Physical Exertion and Emotion to Precipitation of Coronary Thrombi, *J. A. M. A.* **112**: 895, 1939.
2. Wartman, W. B.: Occlusion of Coronary Arteries by Haemorrhage Into Their Walls, *AM. HEART J.* **15**: 459, 1938.
3. Winternitz, M. C., Thomas, R. M., and LeCompte, P. M.: *The Biology of Arteriosclerosis*, Springfield, Ill., 1938, Charles C. Thomas.
4. Cutter, I. S., and Marquardt, G. H.: Studies in Capillary Fragility, *Proc. Soc. Exper. Biol. & Med.* **28**: 113, 1930.

ELECTROCARDIOGRAPHIC CHANGES ASSOCIATED WITH EXPERIMENTAL ALTERATIONS IN BLOOD POTASSIUM IN CATS

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THE increasing interest in electrocardiographic abnormalities which are not due to structural changes in the myocardium has prompted our study of the effect of potassium on the electrocardiogram. An intimate relationship of potassium to automatism and to bioelectric phenomena seems fairly certain, in the light of current knowledge, and numerous investigators have studied the effects of potassium on heart muscle strips, the intact heart, and heart-lung preparations.

Electrocardiograms with concomitant potassium determinations on the intact, unanesthetized subject following potassium administration are rare.

Wiggers¹ produced electrocardiographic changes similar to those due to coronary occlusion by applying with a brush a 20 per cent solution of potassium chloride directly to the ventricle of the dog. Wiggers and his associates^{2, 3} described electrocardiographic changes in dogs following intravenous and intracardiac injections of potassium chloride. These changes varied with the amount of potassium chloride injected and with the site and speed of injection. Concentrations of serum potassium were not determined. Harris and Levin⁴ noted slowing of the human heart and slight diminution in the height of the P waves following the administration of 5 c.c. of 5 per cent potassium chloride solution. They conclude that there is no relation between electrocardiographic changes and concentration of potassium in the serum, but from the data presented this conclusion does not seem justified.

In five experiments on four dogs, Winkler, Hoff, and Smith⁵ found marked changes in the electrocardiogram, with eventual cardiac arrest, following the intravenous administration of 1.12 per cent potassium chloride solution at the rate of 10 c.c. per minute.

In the present study the potassium chloride was given intraperitoneally because Zwemer and Truszkowski⁶ had found that this procedure gave more predictable results and smoother blood potassium curves.

MATERIALS AND METHODS

Eight normal cats were prepared for electrocardiographic observation, using the three standard leads. One or two control electrocardiograms were taken, and

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Received for publication May 28, 1939.

whole blood was obtained for determination of potassium content by the Truszkowski-Zwemer method.⁷ Whole blood determinations are permissible in the cat, since the potassium contents of cells and plasma rise and fall together and are not so widely different as in other species.⁸ Potassium chloride (10 per cent solution) was then injected intraperitoneally into seven of the animals, and 10 per cent sodium chloride solution into the eighth as a control. Repeated whole blood samplings and electrocardiograms were taken at intervals of from five to fifteen minutes until death or apparent recovery. If death ensued, blood from various vessels (cf. Zwemer and Pike⁹) and fluid from the pericardium and cerebrospinal system were collected for determination of potassium content. The specific gravity of the blood was measured by the falling-drop method of Barbour and Hamilton.¹⁰ Three cats given potassium chloride recovered. One had been given a sublethal dose, another was treated with a large amount of physiologic saline, and the third was injected with eschatin.*

RESULTS

The outstanding results in the individual animals are given below, and the chief effects of potassium on the electrocardiogram are then briefly summarized.

Specific data are given in Tables I and II, and illustrated by Figs. 1 to 5.

1. Cat 3732.—After the administration of 938 mg. of potassium chloride per kg. (in 10 per cent solution) intraperitoneally, the blood potassium content showed a gradual rise from 35.2 to 71 mg. per cent. Electrocardiograms taken at ten-minute intervals showed progressive inversion of the T waves in Leads II and III. These changes were marked; the waves, which had been normally upright, became deeply inverted. When the blood potassium content reached 47.9 mg. per cent (30 minutes after injection), intraventricular block appeared, and the QRS complexes assumed the appearance of those which are typical of bundle branch block. Subsequent records showed a marked increase in the intraventricular block, and what was probably complete auriculoventricular block with auricular asystole or auricular fibrillation. The intraventricular block increased, and the ventricular rate was very slow in the last record obtained before death, seventy minutes after injection.

2. Cat 3734.—After the administration of 963 mg. per kg. of potassium chloride intraperitoneally, in 10 per cent solution, the blood potassium content rose from 22.8 to 90 mg. per cent. Electrocardiograms taken at five- and ten-minute intervals showed, at first, flattening and a tendency to inversion of the T waves in Leads II and III. Partial intraventricular block was first noted when the blood potassium level was approximately 43 mg. per cent. When the blood potassium content rose above 66 mg. per cent, complete auriculoventricular block appeared, with occasional paroxysms of ventricular

*For which we take this opportunity to thank Parke, Davis, and Company.

TABLE I
SUMMARY OF ELECTROCARDIOGRAMS AND BLOOD STUDY PROTOCOLS; EKG CONTROL MEASUREMENTS AND MOST IMPORTANT SUBSEQUENT CHANGES

NO. AND PROCEDURE	RESULT	BLOOD K (MG. %)	BLOOD SP. GR.	RHYTHM	VEN. RATE	P MM.	P-R SEC.	AXIS	QRS DUR.	QRS VOLT	T ₁	T ₂	T ₃
No. 3732 938 mg. KCl/Kg.	death in 70 min- utes	control 35.0 maximum 72.0 4 deter.		normal to com- plete A-V block and aur. fib. or asyst.	252 to 38	2 to 3 to 0.2	.06 fib. -	none to rt.	.01 to .21	6.5 10.7 to 15.6	iso. to -3 to +1.3	+4.1 to -8 to -13.3	+1.2 to -5 to -16.2 +1.3
No. 3734 963 mg. KCl/Kg.	death in 94 min- utes	control 23.0 maximum 66.0 death 110.0 11 deter.		normal to aur. asyst. to ven. tachysyst. to ven. fib.	160 to 200 to fib.	1 to 1.5 to -	.09 to .05 to -		.01 to .14	4.2 to 5 to 10.4	±6 to +0.8 to -4	+1 to +1.8 to +6	+1.3 to +2.2 to +8
No. 3743 800 mg. KCl/Kg.	death in a convulsion in 140 min.	control 40.0 maximum 59.2 9 deter.	con- trol max. later	normal to inc. A-V block to aur. fib. or standstill	175 to 190 to	1.5 to 3 to	.08 to inc. block	rt. to ?	.03 to .30	8.5 to 6 19	iso. to +9	+1.2 to +25	+1.2 to +0.7
No. 3744 600 mg. KCl/Kg.	death in 6 hours and 50 min- utes	control 31.8 maximum 90.2 9 deter.	contr. 1.048 max. 1.060	normal to aur. fib. to aur. and ven. stand.	180 to 16	2 to -	.08 to aur. fib.	none	.03 to .12	9 to .12	iso. to -4.5	±1 to -6 to +5	+1 to -7 to +3

TABLE I—CONT'D

No. 3752 400 mg. KCl/Kg.	apparent recovery after 4 hr. 15 min.	control maximum 34.5 20.5 10 deter.	19.5 contr. max. final	1.052 max. 1.053	normal to partial A-V block to aur. or ven. tach. to normal	180 to 260 170	2 to - 2	.07 to .10 to .06	rt. to left	.03 to .07	4 to 10 to 7	+5 to -3 to iso.	+2 to +8 to +2	+2.4 to +10 to +1.5
No. 3752 200 mg. KCl/Kg.	nearly re- covered after 1 hr. 37 min.	control maximum 37.8 28.8 6 deter.	29.7 contr. max. final	1.053 max. 1.055 1.053	normal	170 to 210	2 to 3 2.5	.06 to .08 to .06	none to left none	.03 to left	7 to 3 to 5	iso. to +3 to +1.5	+2 to +3 to +1.5	+1.5 to +2.5 to +1
No. 3755 600 mg. KCl/Kg. followed by 30 c.c. adrenal cortex extract	recovery after 2 hr. 45 min.	control maximum 43.7 29.8 1 week later	23.7 contr. max. final 1 wk. 17	1.053 max. 1.061 1.059 1.051	normal to partial A-V block, aur. stand. to ven. fib. to ven. tach. to aur. stand.	136 -70 -280 95	2 to 0.7 2	.09 to .14 to 0.11	none to left none	.04 to .20 to .04	5.5 to 12 to 5	iso. to -2.3 to +5	-8 to +6.5 to -6	-8 to +8 to -1
No. 3754 600 mg. KCl/Kg. followed by 500 c.c. phys. saline	almost com- plete re- covery in -2 hr.	control maximum 44.3 26.9 17 deter.	23.3 contr. max. final	1.053 max. 1.060 1.042	normal to partial A-V block to aur. stand. to A-V block to normal	167 to 260 200	1.2 to 3 to 1.5	.09 to .11 to .10	rt. to left to rt.	.03 to .12 to .03	8 to 9 to 7	iso. to -1.0 to +6	+2 to +5 to +1.3	+1 to +6 to +1

TABLE II
DETAILED PROTOCOL OF EXPERIMENT ON CAT No. 3755 (600 Mg. KCl/KILO, THEN ADRENAL CORTEX EXTRACT)

TIME AFTER INJECTION	BLOOD K	SP. GRAV. CAP. BLOOD	RHYTHM	P	P-R	QRS DUR.	AXIS DEV.	QRS I	QRS II	QRS III	T ₁	T ₂	T ₃	REMARKS
Control	23.7	1.0526	Tach.	136	2.0	.09	.04	No	+1	+4.7	+5.5	0	-.8	28 c.c. 10% KCl injected intraperitoneally.
-KCl														
10 min.		1.0569	Tach.	134	2.0	.09	.05	No	+1.2	+4	+1.2	0	-1	-.8
15 min.	34.5	1.0581	Partial A-V bl.	105	1.0	.14	.09	No	+3.5	+12	+9	-1.7	-1	+6
25 min.			Slower											tricular conduction. Marked changes.
30 min.	43.4	1.0583												Left bundle branch block now present, with wide QRS, coupling, and questionable ventricular fibrillation.
35'	42.8	1.0578	Complete aur. standstill											Marked increase in abnormalities.
40'			? V. fib.	75		.16	Lt.	+2.5	-6	-7	-1.5	+6.5	±8	
42'			Aur. standstill	170		.12	Lt.	+3	+1	-10	-2	+4.5	±8	Lead III shows wider QRS with more rapid rates.
50'	45.5	1.0583	to tach.	120		.16			-3					
55'		1.0613	Runs of ? V. tach.											Sinus rhythm has appeared again and bundle branch block is less marked. Marked improvement.
57'			Tach.	115	.7	.09	.14	Lt.	3.3	-3	+1	-2.3	+5	+7
50'	45.4	1.0601 (h)												Intracardiac injection 10 c.c. eschatin.
1°30'	(h)		V. fib. V. tach.	220			1.16	Lt.?		-3	-6	±4.5	±2	Ventricular fibrillation. Marked increase in EKG abnormalities.
1°5'														10 c.c. eschatin intramuscularly.

tachycardia. Ventricular fibrillation appeared ninety minutes after injection and was followed by death.

3. Cat 3743.—The animal died in a convulsion two hours and twenty minutes after an intraperitoneal injection of 800 mg. per kilo. Gradual increases in the blood potassium level were accompanied by intraventricular block, followed by auriculoventricular block with what was probably auricular flutter.

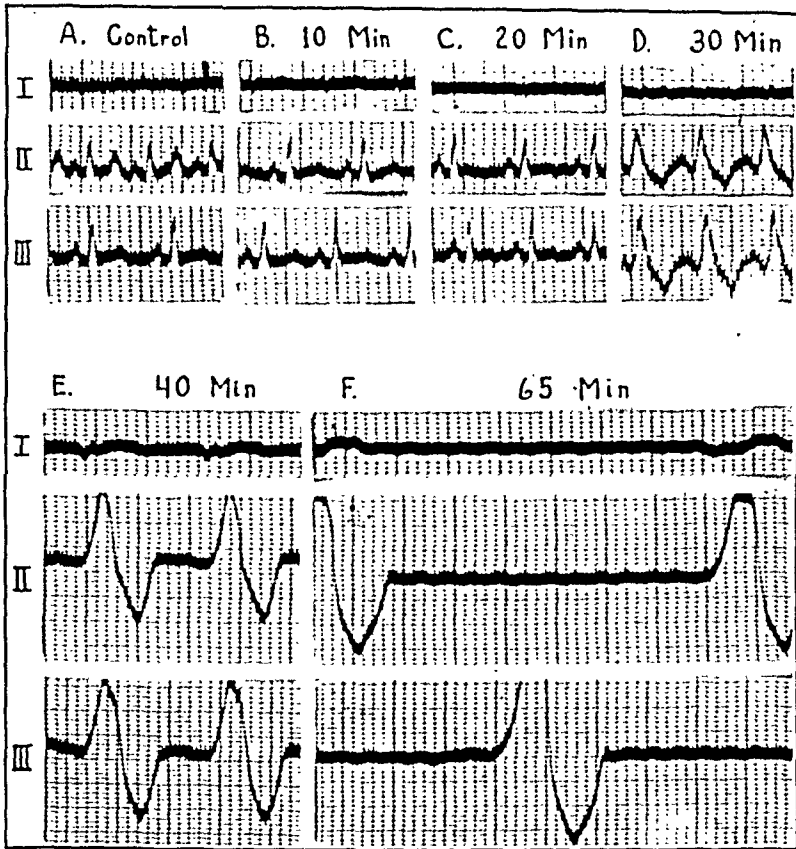


Fig. 1.—Cat 3732. Records taken before and after intraperitoneal injection of 938 mg. of potassium chloride per kilo in 10 per cent solution show progressive inversion of T waves in Leads I and II, followed by intraventricular block and either auricular standstill or auricular fibrillation with complete auriculoventricular block. The tracings were taken with standard technique. The fine vertical lines fall every .04 second, and the fine horizontal lines represent a string deflection of 0.1 millivolt. Blood potassium levels were: control, 35.2 mg. per cent; 47.9 mg. per cent at 30 minutes; 71.2 mg. per cent at 55 minutes. At death, the serum potassium was 72.2 mg. per cent.

4. Cat 3744.—Progressively increasing intraventricular block, auricular fibrillation, and, finally, auricular and ventricular standstill were observed over a period of six hours and fifty minutes following the intraperitoneal injection of 600 mg. per kg. of potassium chloride solution. The electrocardiographic abnormalities increased in spite of a slight decrease in the blood potassium level after the first ninety minutes.

5. Cat 3752.—Sublethal doses of potassium chloride produced transient electrocardiographic changes. Injection of 400 mg. per kg.

produced intraventricular and auriculoventricular block and ventricular tachycardia, with a return to normal four hours and fifteen minutes after injection. Immediately after recovery, a second injection of 200 mg. per kilo caused a rise of 8.1 mg. per cent in the blood potassium level, which was associated with partial auriculoventricular block and minor T-wave variations.

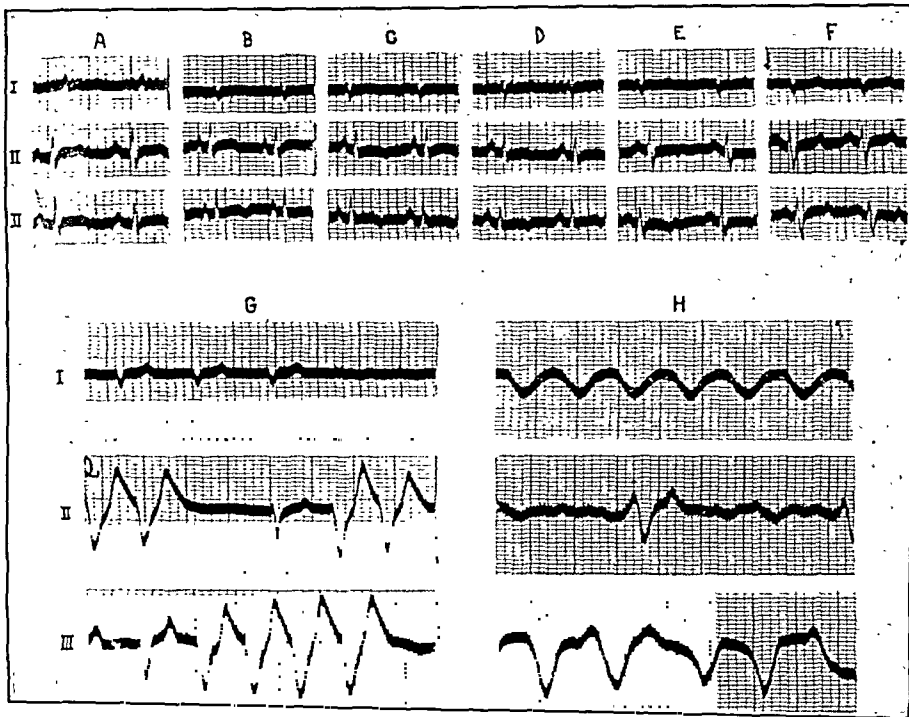


Fig. 2.—Cat 3734. After the intraperitoneal injection of 963 mg. of potassium chloride solution per kilo, tracings show T-wave changes, followed by intraventricular block, auricular standstill, irregular ventricular tachysystole, and ventricular fibrillation. A to H show control and tracings taken at 10, 20, 30, 50, 70, 80, and 90 minutes. Approximate potassium values for tracings A to F were: 22.8, 28.5, 35.8, 35.2, 43, and 59.6 mg. per cent.

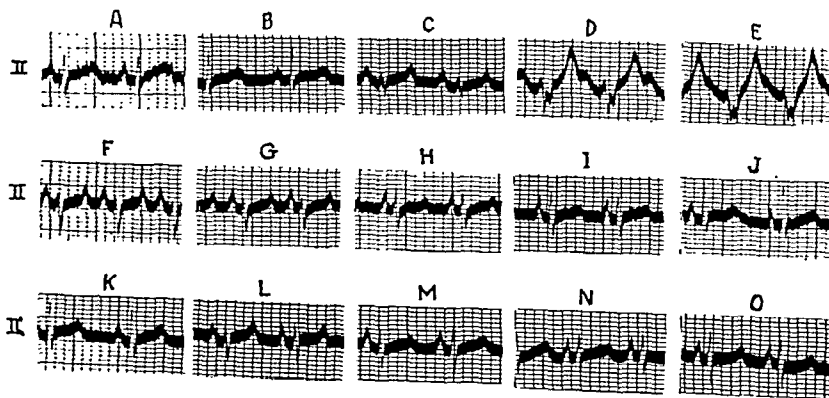


Fig. 3.—Cat 3752. Only Lead II is shown. After injection of 400 mg. of potassium chloride solution per kilo, tracings A to E show the development of partial auriculoventricular and intraventricular block, followed by return to normal. Subsequently, a smaller dose (200 mg. per kilo) caused only slight changes in rate, voltage, and P-R interval, again followed by return to normal (J to O). Timing of tracings A to O is as follows: control, 5, 25, 40, 60, 90, 115, 130, and 230 minutes; second control (J), 15, 30, 45, 60, and 90 minutes. Approximate corresponding potassium levels, in order, are: 19.5, 23.6, 30.7, 32.9, 34.5, 34.0, 30.0, 27.4, 20.5, 29.7, 37.8, 33.0, 33.7, 34.4, and 30.3 mg. per cent.

6. Cat 3755.—Injection of 600 mg. per kg. of potassium chloride solution caused intraventricular and partial auriculoventricular block, followed by complete auricular standstill and periods of ventricular fibrillation, tachycardia, and tachysystole. Recovery followed intramuscular injection of 10 c.c., and intracardiac injections of 20 c.c., of adrenal cortical extract (Parke, Davis, and Company).

7. Cat 3754.—After the appearance of auriculoventricular and intraventricular block caused by injecting 600 mg. of potassium chloride solution per kg., 500 c.c. of physiologic saline were administered intraperitoneally. This was followed by a return almost to normal of both the blood potassium level and the electrocardiogram in less than two hours after the potassium chloride had been injected.

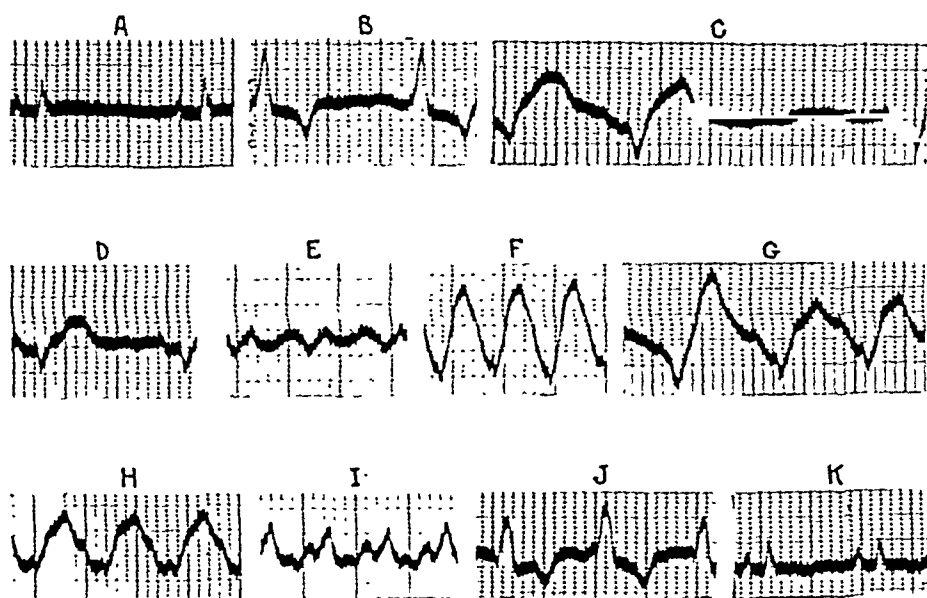


Fig. 4.—Cat 3755. Only Lead II is shown. After administration of 600 mg. of potassium chloride solution per kilo, intraventricular block, partial auriculoventricular block, ventricular tachycardia, irregular ventricular tachysystole, auricular standstill, and the final return to normal are shown. This animal received 10 c.c. of eschatin one hour after the potassium chloride injection, and another 10 c.c. sixty-five minutes later, but with questionable benefit. The tracings, in order, show control, 25, 40, 57, 63, 70, 91, 129, 140, 155 minutes, and 1 week after potassium chloride. The approximate corresponding blood potassium levels are 23.7, 40.4, 44.1, 45.4, 46.0, 45.1, 48.0, 44.6, 43.7, and 29.8 mg. per cent.

8. Cat S-7.—As a control, 27 c.c. of 10 per cent sodium chloride solution (600 mg. per kg.) were injected intraperitoneally. Records taken at half-hour intervals showed no change other than a slight acceleration in rate. The blood potassium level stayed practically constant, varying only between 21.7 and 20.7 mg. per cent.

The relation of potassium administration to changes in the electrocardiogram may be summarized as follows:

Heart Rate.—The effect on the rate was inconstant before A-V block (slowing), or ventricular tachycardia, or sinoauricular tachycardia appeared. Early variations in rate could have been caused by nervous excitement.

P Waves.—The P waves decreased in amplitude by about 1 mm., in two instances, before they disappeared. They disappeared in all cases in which the cat received 600 mg., or more, of potassium chloride per kg. The blood potassium level at the time of the disappearance of the P waves and appearance of auricular standstill was quite variable, ranging from 36.4 to 90.2 mg. per cent.

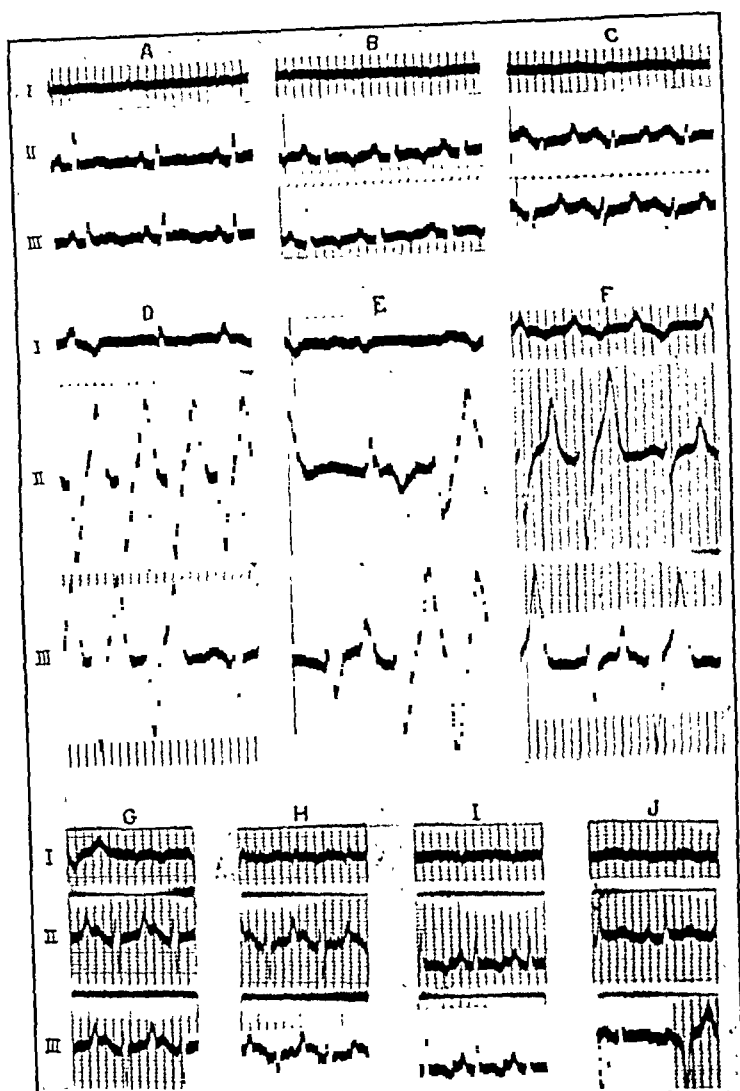


Fig. 5.—Cat 3754. Tracings A to F show reversal of T waves and development of intraventricular and partial auriculoventricular block and ventricular tachysystole after injection of 600 mg. of potassium chloride solution per kilo. Fifty minutes after the potassium chloride administration, an intraperitoneal infusion of 500 c.c. of physiologic saline was started. Tracings F to I show a fairly rapid subsequent recovery. In order, the records show: control, 8, 20, 30, 45, 63, 80, 94, and 110 minutes, and J, 1 week after potassium chloride. The approximate corresponding blood potassium levels are: 23.9, 31.0, 35.5, 36.4, 40.2, 93.3, 37.0, 36.1, 33.1, and 26.9 mg. per 100 ml.

P-R Interval.—Partial A-V block occurred in all the experiments. It was first observed when the blood potassium level ranged from approximately 30.7 to 66 mg. per cent, with an average of about 45 mg. per cent. In the four recovery experiments it disappeared at varying levels, either higher or lower than that at which it was first observed.

QRS Complexes.—The voltage of QRS became lower in three experiments and higher in two, in the early stages of poisoning before intraventricular block appeared. The blood potassium content at the time of the changes in voltage ranged from 30.7 to approximately 44 mg. per cent. Intraventricular block was observed in all the experiments, appearing with a blood potassium range of approximately 31 to 55 mg. per cent, averaging about 42 mg. per cent.

T Waves.—Flattening or inversion of the T waves (especially in Leads II and III) occurred in four experiments before the appearance of intraventricular block. In these animals the blood potassium ranged from 28.5 to approximately 44 mg. per cent, with an average of about 36 mg. per cent. Marked T-wave changes eventually occurred, as would be expected with the appearance of intraventricular block. Ventricular standstill, or so-called ventricular fibrillation,⁴ was observed in four experiments, the blood potassium ranging from 55.3 to 109.7 mg. per cent. Ventricular tachysystole was observed in four experiments, with blood potassium levels varying from 40.2 to approximately 57 mg. per cent.

COMMENT

Our results confirm the findings of Wiggers¹¹ and Winkler, et al.,⁵ in respect to the abnormalities in the electrocardiogram following potassium administration. They extend the observation that many of the changes may be reversed.

The sequence of the various electrocardiographic abnormalities is fairly uniform in each experiment, as are the potassium changes. However, the relative elevation of blood potassium above the control level showed a less close relationship to the electrocardiographic changes in the different experiments than did the actual blood potassium level. Neither the dosage of potassium chloride nor the rapidity with which electrocardiographic changes occurred seemed to be exactly related to the potassium level at which the changes took place.

The similarities between the abnormalities shown in our electrocardiograms and those produced in muscle-strip preparations in which the potassium content of the perfusion fluid was the only variable^{12 a, b, c, d, e} suggest that our electrocardiographic changes may well have been due chiefly to hyperpotassemia. The actual responsibility of potassium for the changes in the electrocardiograms can only be estimated, with our present knowledge, since changes in the concentration of other ions during hyperpotassemia may play an important part. Blood concentration per se is probably not important, as we found no relationship between blood specific gravity and electrocardiographic changes in five of our experiments.

The blood potassium levels reported in the present experiments are not purely of pharmacologic interest, since equally high levels have been

found in cats after the experimental production of intestinal obstruction,¹³ intestinal fistulae,¹⁴ shock,¹⁵ and adrenal insufficiency.^{16 a, b, c} In the last-named syndrome, Nicholson and Soffer¹⁷ noted slowing of the heart rate and auricular fibrillation in eight adrenalectomized dogs whose blood potassium levels were elevated. In two of the animals, normal rhythm was restored after the administration of 200 c.c. of physiologic salt solution.

In certain clinical conditions, changes in the electrocardiogram may be occasioned by potassium release from damaged cells, especially if the general condition of the individual be poor. Unpublished observations by Chamberlain, and a report of a case of intestinal obstruction by Scudder, Zwemer, and Whipple¹⁸ would indicate that this is true.

Addendum

Since this paper was written, two papers have appeared calling attention to changes in the electrocardiogram in adrenal insufficiency concomitant with elevations in serum potassium. Hall, G. E., and Cleghorn, R. A.: Cardiac Lesions in Adrenal Insufficiency, *C. M. A. J.* 39: 126, 1938. Thompson, W. A. R.: Potassium and the T Wave of the Electrocardiogram, *Lancet* 1: 808, 1939.

CONCLUSIONS

1. Experimental increases in the blood potassium content in the cat are associated with abnormalities in the electrocardiogram.

2. In order of appearance, the usual changes are: lowering or inversion of T waves, decrease or increase of QRS voltage, auriculo-ventricular and intraventricular block, auricular standstill or auricular fibrillation, ventricular tachycardia or tachysystole, ventricular fibrillation, and ventricular standstill.

3. The electrocardiographic abnormalities are reversible, and parallel roughly the return of the blood potassium content to normal when a sublethal dose is given, or following the administration of physiologic saline or adrenal cortex extract.

4. The potassium levels at the time electrocardiographic changes appear vary in different cats. This suggests that factors other than blood potassium may also be important.

5. Potassium administration produces marked abnormalities in the electrocardiogram when the blood potassium content is considerably below the level reached in experimental adrenal insufficiency, intestinal obstruction, or intestinal fistula.

REFERENCES

1. Wiggers, C. J.: Monophasic and Deformed Ventricular Complexes Resulting From Surface Applications of Potassium Salts, *AM. HEART J.* 5: 346, 1930.
2. Idem: Studies on Ventricular Fibrillation Produced by Electric Shock; Action of Antagonistic Salts, *Am. J. Physiol.* 93: 197, 1930.
3. Wiggers, C. J., Bell, J. M., and Paine, M.: Studies of Ventricular Fibrillation Caused by Electric Shock, *AM. HEART J.* 5: 351, 1930.

4. Harris, I., and Levin, D. A.: The Effects Upon the Human Electrocardiogram of the Introduction of Ca and K Into the Blood, *J. Physiol.* 89: 153, 1937.
5. Winkler, A. W., Hoff, H. E., and Smith, P. K.: Electrocardiographic Changes and Concentration of Potassium in Serum Following Intravenous Injection of Potassium Chloride, *Am. J. Physiol.* 124: 478, 1938.
- 6a. Zwemer, R. L., and Truszkowski, R.: The Importance of Corticoadrenal Regulation of Potassium Metabolism, *Endocrinology* 21: 40, 1937.
- 6b. Truszkowski, R., and Zwemer, R. L.: Experimental Alterations in Blood Potassium, *Acta Biol. Exper.* 12: 1, 1938.
7. Truszkowski, R., and Zwemer, R. L.: Determination of Blood Potassium, *Biochem. J.* 31: 229, 1937.
8. Truszkowski, R., and Zwemer, R. L.: Cortico-adrenal Insufficiency and Potassium Metabolism. II. Blood Potassium in Normal and Adrenalectomized Cats, *Biochem. J.* 30: 1345, 1936.
9. Zwemer, R. L., and Pike, F. H.: Effects of Nerve Excitation on Potassium in Body Fluids, *Ann. of the New York Acad. Sci.* 37: 257, 1938.
10. Barbour, H. G., and Hamilton, W. F.: The Falling Drop Method for Determining Specific Gravity, *J. Biol. Chem.* 69: 625, 1926.
11. Wiggers, C. J.: *Physiology in Health and Disease*, Ed. 2, Philadelphia, pp. 96, 471, 1937, Lea and Febiger.
- 12a. Busquet, H., and Pachon, V.: Sur le mecanisme musculaire de l'action cardioinhibitrice du potassium, *Compt. rend. Soc. de Biol. Paris* 62: 785, 1907.
- 12b. Busquet, H.: Le paradoxe du potassium sur le coeur isolé de Lapin, *Compt. rend. Soc. de Biol. Paris* 85: 1142, 1921.
- 12c. Chu, H. P., and Sollman, T.: The Autonomic Rhythm of the Turtle Heart Strips as Influenced by the Regional Gradient and Various Conditions, *Am. J. Physiol.* 74: 451, 1925.
- 12d. Howell, W.: An Analysis of the Influence of Sodium, Potassium and Calcium Salts of the Blood on the Automatic Contractions of Heart Muscle, *Am. J. Physiol.* 6: 181, 1902.
- 12e. Kolm, H., and Pick, E. P.: Ueber die Bedeutung des Kaliums fur die Selbststeuerung des Herzens, *Pflueg. Arch. f. d. ges. Physiol.* 185: 235, 1920.
13. Seudder, J., Zwemer, R. L., and Truszkowski, R.: Potassium in Acute Intestinal Obstruction, *Surgery* 1: 74, 1927.
14. Seudder, J., and Zwemer, R. L.: The Effect of Complete Intestinal Fistula on Blood Potassium, *Surgery* 2: 519, 1927.
15. Zwemer, R. L., and Seudder, J.: Blood Potassium During Experimental Shock, *Surgery* 4: 510, 1928.
- 16a. Bauman, E. J., and Kurland, S.: Changes in Inorganic Constituents of Blood in Suprarenalectomized Cats and Rabbits, *J. Biol. Chem.* 71: 281, 1927.
- 16b. Hastings, A. B., and Compere, E. L.: Effect of Bilateral Suprarenalectomy on Certain Constituents of the Blood of Dogs, *Proc. Soc. Exper. Biol. and Med.* 28: 376, 1931.
- 16c. Zwemer, R. L., and Sullivan, Ruth: Blood Chemistry of Adrenal Insufficiency in Cats, *Endocrinology* 18: 97, 1934.
17. Nicholson, W. M., and Soffer, L. J.: Cardiac Arrhythmias in Experimental Suprarenal Insufficiency in Dogs, *Bull. Johns Hopkins Hosp.* 56: 236, 1935.
18. Seudder, J., Zwemer, R. L., and Whipple, A. O.: Acute Intestinal Obstruction. Evaluation of Results in 2150 Cases; With Detailed Studies of 25 Showing Potassium as a Toxic Factor, *Ann. Surg.* 107: 161, 1938.

RUPTURED POPLITEAL ANEURYSM

REPORT OF FOUR CASES

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NEXT to the arch of the aorta, the popliteal artery is the vessel most commonly the site of aneurysm. In contradistinction to the aorta, it is readily accessible to surgical treatment. Syphilis and arteriosclerosis are the common etiologic agents of the nontraumatic variety of aneurysm. Trauma or strain may cause aneurysm due to either agent to rupture. The factor precipitating the rupture may have been so trivial as to have been unrecognized or forgotten. The rupture may thus appear to have been spontaneous, as with aneurysm of the aorta. The popliteal artery is situated at a point where it is subjected repeatedly to severe strain, especially in laborers. This fact probably accounts for the predilection of aneurysm for this artery, and for the frequent ruptures. When rupture, either of a pathologically weakened artery or of a normal one, occurs as the result of a penetrating wound, a false aneurysm forms. This consists of a blood clot without walls other than the surrounding muscles and fascia. The four cases to be reported illustrate many of the important points in the diagnosis, and how the circulation becomes re-established, when rupture of a peripheral artery, such as the popliteal, occurs.

REPORT OF CASES

CASE 1.—This case was first reported in 1936. The patient, M. M., a negro laborer, aged 49 years, entered Gallinger Municipal Hospital for the first time on June 20, 1935, complaining of pain and swelling of the right leg. About one month previously this leg had been struck behind the knee by a falling tub. Prior to that time he had not been aware of any trouble in the leg. The injury did not disturb him much at the time, but fairly rapidly a swelling developed in the popliteal fossa and became moderately painful. In a few days the whole leg became swollen and painful. The swelling subsided gradually to about half of its maximum. The patient had had a penile lesion at the age of 16 years and gonorrheal urethritis later, and two years before he had been told that he had high blood pressure. Physical examination revealed, besides the changes in the leg, some dental caries, a few subcrepitant râles at the bases of the lungs, more than moderate enlargement of the heart, a loud systolic precordial murmur, and a blood pressure of 150/100. In the right popliteal region there was a slightly expansile tumor which projected about 5 cm. posteriorly. It was firm and immovable, and a soft systolic murmur was audible directly over it. The foot and ankle were moderately edematous. The Kahn test

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Read at the Fifteenth Annual Meeting of the American Heart Association, St. Louis, Mo., May 13, 1939.

Received for publication June 2, 1939.

on the blood was negative on three occasions. Other laboratory tests showed nothing abnormal. Hospitalization lasted three weeks. The temperature and pulse rate were normal, and the condition of the right leg did not change. The patient refused operation and returned home. The diagnosis was aneurysm of the right popliteal artery.

He returned Oct. 21, 1935. The whole right leg, below the middle of the thigh, had become much larger, was semiflexed at the knee, and could not be straightened. Walking was impossible. The greatest swelling was in the popliteal space. Here there was a small fluctuant area. A small needle was inserted in this region, and blood was easily aspirated. The systolic bruit was still audible. The leg felt warmer than the unaffected one. The mouth temperature was elevated less than a degree. Examination of the blood and other laboratory procedures showed nothing abnormal, including again the Kahn test on the blood. A roentgenogram of the chest revealed a somewhat dilated and tortuous aorta and that the heart was moderately enlarged and of the "aortic type."

Arteriograms were made by means of thorium dioxide sol (Thorotrast Heyden). They showed that the femoral artery faded out just above the popliteal fossa. Just behind the knee joint there was a semilunar space filled with the contrast medium. This appeared to be peripherally located in the middle of a large, soft-tissue tumor. Some distance below this both the anterior and posterior tibial arteries were visible, together with some small branches.

On another day, thorium dioxide was injected into the femoral vein in a similar manner, and roentgenograms were made. As the vein passed the popliteal mass it appeared to be compressed peripherally, and below the mass it could not be followed very far. Some of the contrast medium previously injected still remained in the tumor.

The case was considered to be one of a popliteal aneurysm too large to be treated except by amputation of the extremity. Consequently, on November 2, amputation was performed at the middle of the thigh. The postoperative course was uneventful, and the patient left the hospital on December 15 with the stump thoroughly healed.

The amputated extremity was carefully dissected to isolate the vessels and the aneurysm (Fig. 1). The popliteal artery and vein were followed distally. They appeared to be normal. A short distance above the knee joint the continuity of the artery apparently ceased. Just below this point a large, dark blood clot, measuring about 10 by 8 by 8 cm., had formed and pushed the muscles posteriorly. The muscles were infiltrated with blood. After further dissection it was observed that there was a false sac about the clot, composed of a layer of compressed coagulum, and that on one side there was a broad ribbon of fibrous tissue with a smooth inner surface. The latter was continuous with the popliteal artery, and about 5 cm. below the apparent end of this artery a lumen was found in the fibrous wall which was undoubtedly the lower orifice of the popliteal artery in the wall of a ruptured aneurysm. A hollow probe was inserted through this lumen and passed down the remaining 7 cm. of the popliteal artery into the anterior tibial artery. The branching of the popliteal artery occurred about 2 cm. below the aneurysmal sac. The popliteal vein was compressed by the side of the artery external to the aneurysmal sac.

Microscopic sections were made through the popliteal artery and through various parts of the wall of the ruptured aneurysmal sac, including one across the lower portion of the popliteal artery and vein. These did not reveal any definite evidence of syphilis. The popliteal artery was only moderately atherosclerotic. The wall of the aneurysm was composed of hyaline connective tissue, and sections stained with acid orcein showed interrupted narrow bands of fragmented elastic tissue nearer the inner surface of the wall of the sac. The section

through the lower portion of the popliteal artery and vein showed moderate atherosclerosis of these vessels. The artery lay just within the wall of the sac, the vein just lateral to it.

The patient was seen again in the Outpatient Department in January, 1936. The stump was in good condition, but the patient was not feeling well. A large, reniform mass was palpated in the right flank. He entered the hospital three weeks later, but before a definite diagnosis could be made he died of some cerebral complication.

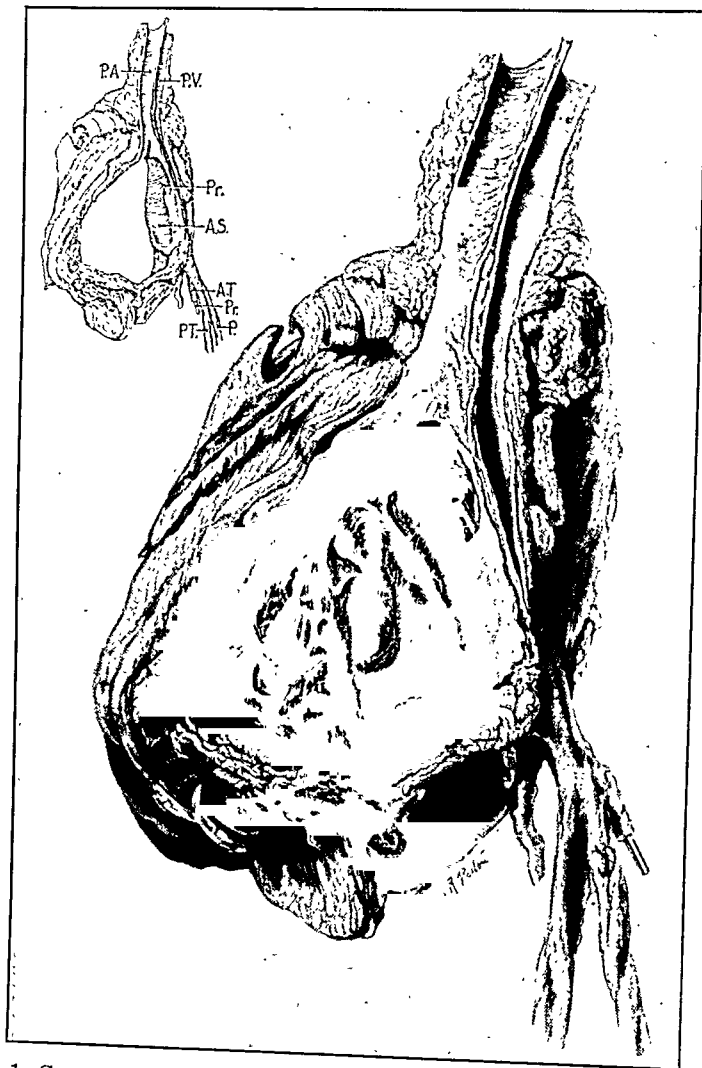


Fig. 1, Case 1.—The ruptured aneurysm, dissected after amputation.

CASE 2.—J. M., a colored man who gave his age as 56 years, but who looked 10 years older, entered Gallinger Municipal Hospital Dec. 11, 1937, because of enlargement of the left leg below the knee. The leg had begun to disturb him just one year before, with a little pain and swelling of the left foot and a sensation as of pins and needles. He rubbed his leg and soaked his foot, but continued to work. The calf began to swell, and by June, 1937, it was quite large. Pain occurred intermittently, usually after eating meat, according to the patient. The swelling finally became so great as to make walking impossible. The only traumata to the leg had been a blow in 1917, and a fall early in 1936. He had had a penile lesion three years before.

Examination showed nothing of importance except a tremendous, fusiform, smooth, stony-hard swelling of the left calf (Fig. 2). This leg was several times larger than the other. The foot was moderately edematous, and the popliteal artery and vessels in the foot could not be felt to pulsate, apparently because of the edema. The skin was dry, roughened, and thick. Roentgenograms showed marked periosteal proliferation of the upper half of the tibia. Arteriograms were unsatisfactory. The blood Kahn reaction was moderately positive (2 plus).

Amputation was performed in the lower third of the thigh, and the patient's recovery was essentially uneventful. Dissection of the specimen showed that the swelling consisted of a tremendous blood clot, in the upper part of which the posterior tibial artery was found to terminate in a dilated portion which was continuous with a false sheath over the clot. The vessel was found again about 15 centimeters lower down. The anterior tibial artery was traced through the edge of the clot. Microscopic sections through the posterior tibial artery showed extensive degenerative changes of a nonspecific nature through the entire wall, and a little thickening of the intima.



Fig. 2, Case 2.—Tremendous enlargement of left calf.

The surgeons had considered that this was probably a case of sarcoma. Arteriograms would have enabled us to make a correct diagnosis. As a matter of fact, ruptured aneurysm was thought of, but was not considered seriously because of the stony hardness of the tumor. However, the shape of the enlargement was more consistent with this diagnosis. It is astounding that there were no serious trophic changes in the extremity caused by compression of the arteries, and only moderate edema from compression of the veins.

CASE 3.—F. B., a negro laborer 35 years of age, entered Georgetown University Hospital Feb. 15, 1938, because of a painful swelling in the left popliteal region. For about five months before admission the left leg and foot had been moderately swollen. The swelling practically disappeared each night. About five weeks before admission a moderately painful "lump" appeared in the left popliteal region. The patient claimed that at first he was able to rub this localized swelling away, but for two weeks it had been growing larger. There was no history of injury of any kind. He had had a penile chancre seven years before, for which a course of treatment had been received at that time.

Physical examination showed nothing important except a rounded, somewhat tender, fluctuant, firm, pulsating mass in the lower part of the left popliteal region, about the size of a large lemon. A systolic thrill and bruit were present directly over the mass. Arterial blood was aspirated from it. Just proximal to the mass there were two, small, tender nodules that felt like enlarged, inflamed lymph nodes. There was slight edema of the leg and foot. Arterial blood-pressure measurements on various occasions showed relatively little difference between the two thighs. The pulsations of the left dorsalis pedis artery were very feeble, and those of the posterior tibial artery could not be felt. There were no trophic changes, and the left leg felt warmer than the right, especially over the mass. The blood Wassermann and Kahn reactions were strongly positive (4 plus).



Fig. 3.

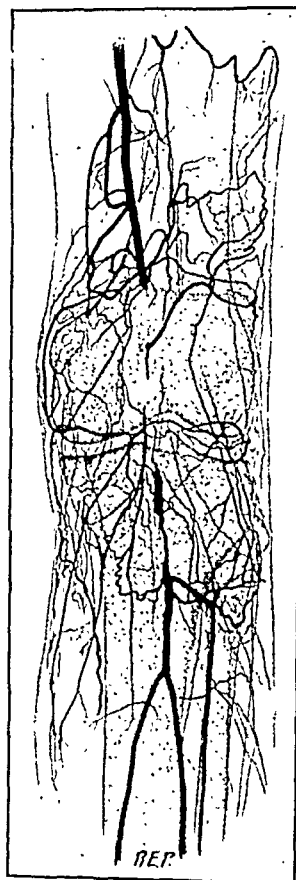


Fig. 4.

Fig. 3, Case 3.—Preoperative arteriogram.

Fig. 4, Case 3.—Exact line drawing of arteriogram made five weeks after operation.

Arteriograms made by means of thorotrast showed, in the first film, narrowing of the shadow of the left popliteal artery to a point (Fig. 3), and, in a second film, the presence of a little thorotrast in the anterior tibial artery above the ankle. These findings were interpreted as evidence of rupture of a small popliteal aneurysm.

Three weeks were utilized in preparation for operation. This consisted in intramuscular injections of bismuth subsalicylate (four in all), the oral administration of saturated solution of potassium iodide, and compression of the left femoral artery against the pubic bone two or three times daily for periods pro-

gressing from ten minutes to one-half hour. During this time the mass became a little larger and firmer, and its pulsations feebler. Blood which was aspirated was darker than originally, but was under good pressure. The oral temperature was normal except on two days, when it rose to 100° F.

On March 19, 1938, operation was performed by Dr. Fred Sanderson. An incision was made over the mass and a false sac exposed. The popliteal vessels were found to be displaced medially. These vessels were isolated and ligated proximal to the mass, after which the mass was incised and found to be a large blood clot, which was removed. It was not considered advisable to attempt to dissect the popliteal artery in order to find the point of rupture, but a portion of the artery distal to the point of ligation was removed, and the incision was closed. Recovery was entirely uneventful. The patient left the hospital just two weeks after the operation.

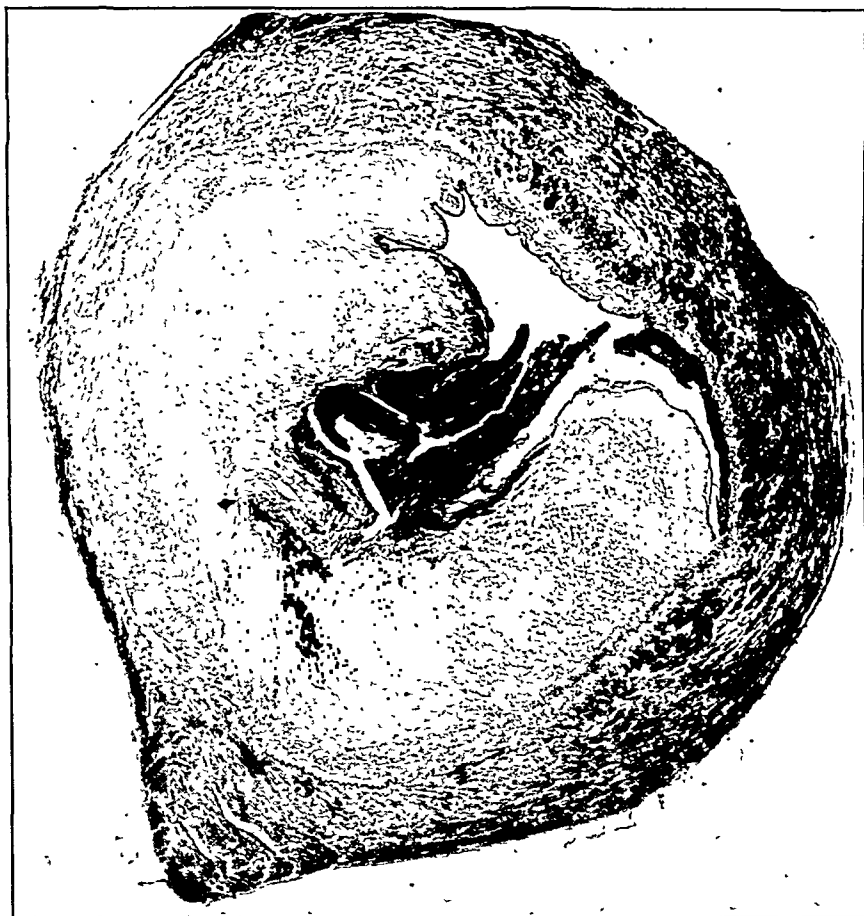


Fig. 5, Case 3.—Cross section of excised portion of popliteal artery, magnified 36 times.

Within a few days pulsations were found to be stronger in the left dorsalis pedis artery and were again felt in the posterior tibial artery. Five weeks after the operation other arteriograms were made. These showed that a remarkable collateral circulation had been established, bridging the gap in the popliteal artery and maintaining blood flow through the main arterial pathways (Fig. 4). In the distal part of the popliteal artery there was an eccentrically narrowed portion which probably indicated localized disease of the vessel.

Microscopic sections of the excised portion of the popliteal artery showed extensive fibrous replacement of the media (Fig. 5). On one side of the wall

there was very little muscle left; on the other side there was destruction of about 50 per cent of the muscle. The greater part of the lumen was filled by light, fibrous, in general sparsely cellular tissue containing practically no blood vessels. This tissue had apparently resulted mainly from proliferation of the intima, rather than from thrombosis within the lumen, although there was a thrombus intimately associated with the free margin. The internal elastic



Fig. 6, Case 4.



Fig. 7, Case 4.—Preoperative arteriogram.

lamina, as stained with acid orcein, was seen to be somewhat disrupted, but to be present around the vessel in a relatively normal position. The adventitia had been stripped from the vessel. There was no evidence of any active inflammatory process in any part of the vessel wall.

CASE 4.—E. J., a negro laborer, aged 37 years, entered Gallinger Municipal Hospital April 18, 1938, because of a painful swelling behind the right knee.

This was first noticed about Jan. 1, 1938, and had gradually become larger until it had attained the size of an orange. He felt it throb with each beat of the heart. The leg could not be extended completely. He had gone to the outpatient clinic of another hospital because of the swelling, and had been given five injections "for his blood" without apparent effect. He had had a penile lesion 15 years before, and had received five injections at that time. Approximately at the same time he had been cut on the medial aspect of the right knee with a crosscut saw, but recovered promptly, and the scar was now well above the knee and in no relation to the swelling. No other injury had been sustained.

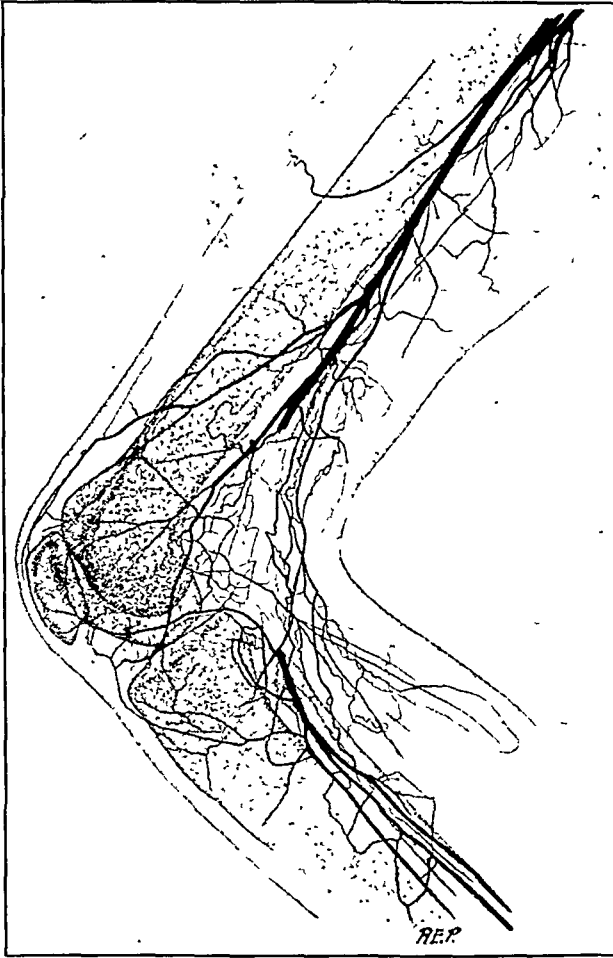


Fig. 8, Case 4.—Exact line drawing of arteriogram made three weeks after operation.

Physical examination showed nothing of interest except for the right leg. A rounded, pulsating mass was present in the popliteal space (Fig. 6), over which a systolic murmur was audible. There were no trophic changes and no edema. The dorsalis pedis and posterior tibial vessels were pulsating feebly. The blood Kahn reaction was strongly positive (4 plus). Arteriograms showed definitely that the popliteal artery had ruptured (Fig. 7). It came to a point in the upper part of the popliteal space; directly behind the knee joint there was a jagged opacity caused by escape of thorotrast, but adjacent to this the popliteal artery was visible again. A fair number of small collateral arteries were present.

Antisyphilitic treatment and intermittent occlusion of the femoral artery were instituted in preparation for operation. An irregular fever of 1° to 2° F. occurred almost daily. The swelling became larger and more painful, and the leg became somewhat edematous.

Operation was performed on May 3, 1938, by Dr. Charles S. White. A large clot was removed from the popliteal fossa, after which the artery was exposed. A small, ruptured aneurysm, less than 2 cm. in diameter, was found. This was resected.

Unfortunately, after the operation there was evidence that the popliteal nerve had been injured, although care had been exercised to avoid it. In a few days dry gangrene appeared in the first and fifth toes. The patient's temperature was normal for three weeks, but the wound became infected and the temperature rose to 103° and 104° F. On June 21 the leg was amputated in the middle of the thigh. The temperature gradually returned to normal, and the stump healed.



Fig. 9, Case 4.—Longitudinal section of the ruptured aneurysm, stained for elastic fibers with acid orcein.

Before the amputation, three weeks after the first operation, arteriograms were again made (Fig. 8). These showed a most remarkable bridging of the resected section of popliteal artery by collateral arteries, so that the function of the popliteal artery was maintained below the knee.

Microscopic sections were made transversely through the popliteal artery and vein just proximal to the ruptured portion, and longitudinally through the artery. The sections were stained with Masson's trichrome. The intima and subintima of the artery were greatly thickened, mainly by a loose, areolar

type of connective tissue containing fibroblasts; in some places this tissue had changed into a dense hyaline substance. The internal elastic lamina was moderately fragmented, but, as a rule, could be traced (Fig. 9). The muscle fibers of the media were separated moderately by fibrous tissue, and in some portions there was considerable infiltration of the media by lymphocytes. The adventitia was composed of dense fibrous tissue containing a few lymphocytes. The popliteal vein was affected in the same way as the artery, but even more so. Its lumen was filled with a clot which was undergoing organization along one side. Two, smaller, medium-sized vessels nearby were so changed as to make it almost impossible to tell whether they were arteries or veins, but one was evidently a branch of the popliteal artery, and the other was probably a vein. Their lumens were practically occluded by subintimal thickening, and their muscular coats were greatly disrupted. The connective tissue between and around the vessels was dense fibrous tissue containing scattered lymphocytes, most numerous in the vicinity of arterioles. In some areas there were considerable collections of erythrocytes. Close to the artery there was a collection of lymphocytes and plasma cells suggestive of a gumma, but nowhere was there the typical perivascular lymphocytic infiltration of the small vessels such as one sees usually in syphilitic vascular disease. As the aneurysm was approached from either direction, the artery became more abnormal, its media being almost entirely replaced by fibrous tissue. The wall of the aneurysm itself was composed of fibrous tissue. Some strands of elastic tissue were imbedded in the wall and constituted the only evidence that this had once been the wall of an artery. These elastic tissue strands were more or less continuous with the internal and external elastic lamina of the artery.

DISCUSSION

The diagnosis of popliteal aneurysm itself is usually not difficult. The presence of a rounded, pulsating, fluctuant mass, with a localized systolic bruit, is always suggestive. In every doubtful case a medium-sized aspirating needle should be inserted to ascertain the nature of the contents of the mass. The diagnosis of rupture of a popliteal aneurysm may not be so easy. When there is a history of a rather rapidly growing swelling, with or without a previous injury, this condition should be thought of. The mass may or may not pulsate. Insertion of an aspirating needle often, but not always, allows the withdrawal of blood or bloody serum. The vessels in the foot often cannot be felt to pulsate. In long-standing cases, such as Case 2, particularly, when the mass has grown large and hard, the diagnosis is most difficult. In doubtful cases arteriography should settle the point. The arterial shadow will end at the site of rupture, and an opacity in the soft tissues will often be seen, indicating escape of contrast medium from the artery. There may be shadows of the tibial arteries at a lower point. In cases of simple aneurysm, arteriograms show no break in continuity and no seepage, although two, or even three, serial films may be necessary to show that blood is flowing through the aneurysm.

Although it may be advisable to try to promote the development of a collateral circulation prior to operation, it is probably wrong to de-

lay operation if the mass is painful and growing rapidly. Apparently, all that is necessary is to remove the clot and to ligate the artery and vein proximal to the point of rupture. Whether a section of the artery should be excised is questionable. In general, the less that is attempted the better the outcome. In Case 3 this procedure was followed, with excellent results. In Case 4 the aneurysm was removed with considerable difficulty, and the nerve was accidentally injured. It is not necessary to ligate the vessel distal to the point of rupture. The question of the advisability of trying to save the limb when the mass has attained a large size and become hard may be raised. Unfortunately, this was not done in Cases 1 and 2. There does not seem to be any reason, however, why the attempt should not be made. If there are no serious trophic changes, there is apparently no way of predicting the outcome.

Of particular interest is the subject of establishment of a collateral circulation. In Cases 1 and 4 the main arteries below the site of rupture were definitely functioning before the operation, as shown by the arteriograms. The question is whether the blood reached these vessels entirely or largely by means of collaterals, or whether it seeped around or through the hematoma to enter the open arteries below. The latter may be the case, since it took longer for the contrast medium to appear in the distal arteries than it should have if it had reached them by collaterals. It is possible, however, that the pressure of the hematoma on small collateral vessels may have slowed the passage of blood through them. In Cases 3 and 4, in which arteriograms were again made, five and three weeks after operation, respectively, there was remarkable bridging of the popliteal arterial defect by numerous collateral vessels, so that the functional integrity of the large artery was maintained. At this time, however, the thorotrast entered the distal part of the artery rapidly, apparently as quickly as if the vessel had been uninterrupted. This method of bridging of defects of large arteries is probably a common one.¹ Apparently, the prevalent idea that a clot usually forms in an artery distal to an area of occlusion is incorrect. Often the vessels remain open and continue to function because of the collateral channels.

Pathologically, the lesions in all four cases were nonspecific. All four men had had chancres, and the serologic tests for syphilis were still positive in three. This fact does not prove that the arterial lesions were of a syphilitic nature. However, in view of all the circumstances, it appears probable that the degenerative changes were the result of syphilitic arteritis. It may be that syphilis can produce lesions of arteries other than those usually described as syphilitic.

Definite trauma had occurred in only one of the four cases. This, a blow on the popliteal fossa, appeared to be the cause of the rupture. In the other cases the rupture was apparently spontaneous.

SUMMARY AND CONCLUSIONS

The popliteal artery is a relatively frequent site for aneurysm. Because of their location, rupture of such aneurysms is comparatively common. This occurs as the result of trivial or unnoticed trauma.

Ruptured popliteal aneurysm should be suspected in any case of progressive and, especially, pulsatile swelling in the popliteal region. Aspiration aids in the diagnosis, but arteriograms are necessary in doubtful cases.

In the four cases reported, pathologic study revealed severe degenerative changes of a nonspecific nature in the artery. All of the patients had syphilis.

REFERENCE

1. Yater, W. M.: Maintenance of the Functional Integrity of Occluded Large Arteries as Demonstrated by Thorotrast Arteriography, *Am. J. Med. Sc.* 104: 372, 1937.

LOUD, MUSICAL, DIASTOLIC MURMURS OF AORTIC INSUFFICIENCY

CLINICAL AND PATHOLOGIC OBSERVATIONS UPON THEIR CAUSE AND THE MECHANISM OF THEIR PRODUCTION

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THE diastolic murmurs of aortic insufficiency are usually soft and blowing in quality, but occasionally they may be strikingly musical and very loud. Their musical quality is suggested by the various descriptive terms that have been applied to them: "cooing of a dove," "buzzing of a saw," "like a cuckoo clock," "humming of a top," etc. It is also shown by recorded heart sounds in which the vibrations are very rapid and regular (Fig. 1). Their intensity is indicated by the fact that the murmurs are often audible to the patient himself and, not infrequently, to the unaided ear of the examiner at some distance from the patient.

These loud, musical, diastolic murmurs have interested clinicians and pathologists for more than one hundred years. So far as we can discover, they were first fully discussed by Hodgkin,¹ who attributed them to retroversion of an aortic leaflet. Recent observers, with one exception,² have largely discarded this and other old explanations and have come to regard a ruptured or torn leaflet as practically the only, or at least the usual, cause of these murmurs. In eleven current textbooks, this is the only explanation advanced; in only one² is retroversion mentioned. We have recently had the opportunity of studying eleven patients who presented these unusual signs and have come to the conclusion that although a rupture or tearing away of a valve leaflet from its commissural attachment can produce these murmurs, this lesion is rare; and that the distinction of being the commonest cause should be accorded to the lesion first clearly described by Hodgkin,¹ and recently again referred to by Scott,² namely, retroversion or eversion of a valve leaflet.*

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Received for publication June 5, 1939.

*We are using the terms "retroversion" and "eversion" of a valve leaflet synonymously. By either of them, we imply that, at some point distal to the attachment of a leaflet to the aortic wall, pathologic processes have caused the distal portion of the valve to become bent downward toward the chamber of the left ventricle (Fig. 2). This is perhaps best illustrated by a longitudinal section through such a leaflet (Fig. 3).

The literature dealing with ruptured aortic valves was reviewed by Howard³ as recently as 1928 and will not be further discussed. We wish to cite certain other papers dealing mainly with other causes of musical diastolic murmurs.

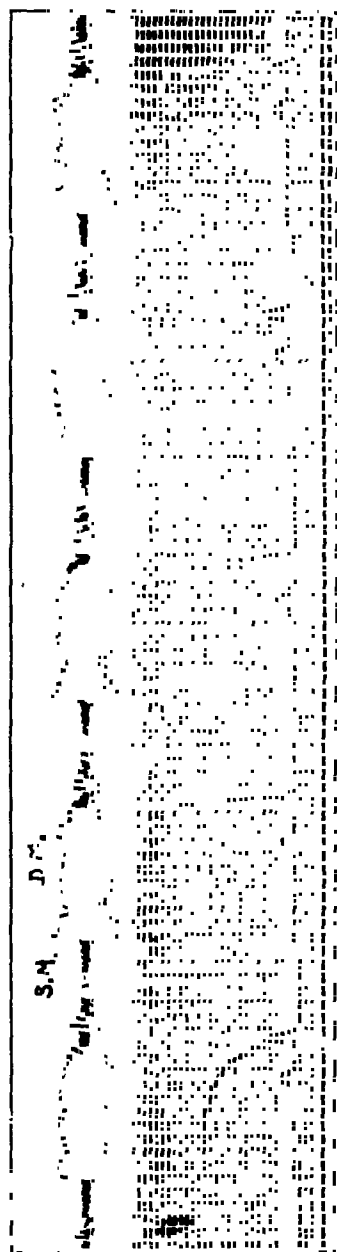


Fig. 1.—Phonocardiogram of a musical diastolic murmur. The diastolic murmur begins immediately after the second sound and continues to the first sound. This is followed by a nonmusical systolic murmur. The vibrations are quite regular and rapid (275 per minute) during most of the diastolic murmur. Toward the end of the murmur, the frequency and intensity diminish.

As we have indicated, the earliest complete discussion of these murmurs that we have discovered is contained in a paper written by Hodgkin in 1829 in which these loud diastolic murmurs are referred to as the "Bruit de scie," and likened to the "cooing of a dove." A necropsy study in one case revealed retroversion of one or two aortic valve leaflets, which was accepted as the cause of the murmur. In this paper, Hodgkin gave credit to Key for first pointing out this

lesion and its significance in 1827. Elliotson,⁴ in 1830, stated that he convinced Hodgkin that Bertin⁵ had first described retroversion. Neither Bertin nor Elliotson, as far as we can determine, definitely associated retroversion with musical aortic diastolic murmurs as Hodgkin did; Elliotson, however, did describe very loud musical murmurs "exactly resembling the cooing of a dove," but he attributed them to mitral lesions.

Hope,⁶ in 1842, felt that loud musical murmurs were not uncommon. He found them associated both with aortic insufficiency and mitral lesions. Peacock,⁷ in 1854, described a very loud, musical, diastolic murmur in a man 65 years old, which "exactly resembled the sound



Fig. 2.—Everted aortic valve leaflet. Note retroversion of the right anterior leaflet (Case 3).

produced by the common cuckoo clock" and could be heard at a distance of several feet from the patient. At necropsy, the aortic valves were thickened, the segments were separated from each other (probably syphilitic?), and the free edge of the right leaflet was retroverted. The loud musical murmurs described by Stokes⁸ (1855), Wunderlich⁹ (1855), and Banks¹⁰ (1857) may have been of the type we are discussing, although their written descriptions leave some uncertainty. Stokes found the murmurs associated with irregular ossification of the aortic orifice; Wunderlich attributed them to an anomalous cord between the ventricular wall and septum, which was put on tension during ventricular filling; and Banks attributed the murmurs

to cribriform aortic valves (one case) and an atheromatous prolongation more than an inch in length, which, stretching up into the aorta, "must have vibrated like the tongue of a Jew's harp" (one case).

More recently, Wilson and Jamieson¹¹ (1918) studied clinically three cases of loud, musical, aortic diastolic murmurs. Two patients gave histories of having been rendered unconscious by the explosions of shells; but, since the murmurs did not become audible until a considerable time later, it was impossible to connect the accidents with the valve lesions. In neither case was there any history or evidence



Fig. 3.—Longitudinal section through aortic leaflet, which is everted (from Case 4). The leaflet is typically everted. Note interruption of the ventricularis elastica and eventual total destruction at point of eversion. V.E., ventricularis elastica; X., loss of elastica in thickened everted leaflet; A., postinflammatory scar tissue. (The fibrosa is irregularly thickened.)

of organic disease which might have weakened the valve. The third patient became conscious of the murmur on the fourth day after being gassed with phosgene, but there was no history of injury or concussion. The valve lesion in this last case was considered by the authors to be of syphilitic origin. The murmurs were all sufficiently loud to be audible to the patients themselves and to the unaided ear of the examiner one to five feet from the chest wall. Since no necropsy examinations were made, no more definite causes of these murmurs could be established.

As we have already stated, Scott, alone of the recent authors, so far as we are aware, has attributed loud musical diastolic murmurs to retroversion of an aortic valve leaflet. He referred to this lesion and to rupture of a valve leaflet as causes of these murmurs. He did not emphasize, as we believe it deserves, that retroversion is the predominant cause of these striking signs.

Clinical and Necropsy Findings.—Of the eleven patients constituting our series, five were studied only in life; six were studied both clinically and at necropsy. The essential findings are summarized in Table I. Some of the facts which require emphasis follow.

The etiology of the aortic insufficiency in all of the necropsy cases was syphilis, for in all there were characteristic aortitis and separation of the commissures. In four of the five patients studied only in life, syphilis seemed to us to be clearly the cause of the aortic insufficiency. In the remaining patient, a boy 11 years of age, the murmur developed during a typical attack of rheumatic fever and was apparently the result of this disease. In the latter patient, bacterial endocarditis was considered as an etiologic factor, but this appeared unlikely after three negative blood cultures and an afebrile course of 2 months.

In every necropsied patient, the right anterior aortic leaflet was retroverted; the posterior leaflet, as well, was retroverted in one (Case 5).

The diastolic murmur in all instances was similar, in that it was musical and loud. Such descriptive terms as the "buzzing of a saw," "cooing of a dove," "humming of a top," etc., quite aptly describe the musical character of these murmurs. While loud, the murmurs were not audible at any distance from the chest wall except in one instance (Case 1), in which the patient's bedfellow was considerably annoyed by the unusual and constant noise. The murmurs were, however, audible to the patients themselves in four instances (Cases 1, 7, 9, and 10). Incidentally, the intensity of the murmur does not necessarily determine whether it will be audible to the patient, for some of the loudest murmurs (to the examiner) were not audible to the patient, and vice versa.

All eleven patients presented marked diastolic thrills. These were of maximum intensity in the second right intercostal space in all but one instance; in Case 5, the thrill could be felt only in the third left intercostal space. It may be of some importance that the posterior, as well as the right anterior, leaflet was retroverted in this patient.

The peripheral signs in all instances indicated free aortic regurgitation. In ten of the eleven cases, there were precordial pain, congestive heart failure, or both. The manifestations were those of severe heart disease, and this diagnosis was substantiated by the outcome, for nine of the patients died while they were under observation in the

hospital. Death was sudden in several instances; usually, however, it came after a rather prolonged period of cardiac failure which set in relatively soon after the murmur was discovered, either by the patient or by a physician.

In a few instances the murmur developed suddenly during strenuous physical effort and was accompanied by severe pain and breathlessness. In other instances the patient became aware of the murmur suddenly, but the development of symptoms, while not coming on with dramatic suddenness, followed shortly.

DISCUSSION

Causes and Etiology of Loud, Musical, Diastolic Murmurs.—From the literature, it is apparent that a number of lesions of different etiologies have at one time or another been thought to be causative of loud, musical, aortic diastolic murmurs. Our own observations lead us to feel that retroversion of the right anterior aortic valve leaflet, produced by syphilitic involvement, is by far the commonest cause of these murmurs, although occasionally some other valve lesion or a different etiologic agent may be responsible. Our reason for attributing to syphilis the predominant etiologic role lies in the fact that in only one instance have we so far found any other disease which might have been a factor.

We are of the opinion that retroversion, rather than rupture or tear of a leaflet, is the usual cause of these striking murmurs, for these reasons: (1) In every patient with a loud, musical, diastolic murmur who came to necropsy, retroversion of the right anterior aortic leaflet was present and was the only constant valvular deformity that furnished a reasonable explanation of the unusual murmur; (2) tear or rupture of a leaflet, generally accepted as the cause of loud, musical, diastolic murmurs at the present time, is, in our experience, a very rare lesion. From 1931 through 1936, 10,100 necropsies were performed at the Philadelphia General Hospital. Except when bacterial endocarditis was present, this material yielded only one example of a torn or ruptured aortic leaflet; the valve leaflet showing this lesion was also retroverted.

It is to be noted that the murmurs in our patients, while sufficiently loud to dominate all other auscultatory findings, were not as intense as some that have been described, because they were not audible at a distance from the patient. It occurs to us that very loud murmurs, such as those described by Wilson and Jamieson,¹¹ for instance, may be the result of some lesion other than retroversion, possibly a torn or ruptured valve leaflet. Our material furnishes no definite data concerning the very loud basal diastolic murmurs. It does indicate, however, that moderately loud, distinctly musical diastolic murmurs have as their predominant cause retroversion of a syphilitic aortic valve leaflet.

Mechanism of Retroversion.—We have had an opportunity of studying histologically only two retroverted valves. There were two changes present in both which probably contribute to the development of retroversion. The first was the characteristic separation of the commissures, which might promote retroversion by permitting the free edge of the leaflet to sag and thus become more susceptible to the regurgitant column of blood. The second was a change in the fibrosa, with loss of the compactly arranged collagen fibers and thickening of the leaflet by inflammatory tissue (Fig. 4). While it is not improbable that both of these alterations may contribute to retroversion and may even be necessary preliminary changes, it seems doubtful if these lesions alone always produce the deformity, for we see both changes in unverted syphilitic valves, although it is our impression that the fibrosal lesions were more marked in the two retroverted valves which we have had an opportunity of studying histologically than in unverted leaflets (Figs. 3 and 4).



Fig. 4.—Longitudinal section through aortic leaflet, without eversion. (From a case of typical syphilitic aortitis and valvulitis). Note continuous black line of ventricular elastica sweeping up on the ventricular surface of the proximal half of the aortic leaflet. While not as thick as in the normal leaflet, it is uninterrupted, and the contour of the leaflet practically normal (Weigert's stain). V.E., ventricularis elastica; F., fibrosa.

It seems probable, therefore, that there are other factors in the pathogenesis of retroversion. One such factor has been proposed by Scott,² who observed a thick, tense, fibrous band running the length

TABLE I
CLINICAL AND PATHOLOGIC FINDINGS IN ELEVEN CASES OF AORTIC INSUFFICIENCY WITH LOUD, MUSICAL, DIASTOLIC MURMURS

CASE NO.	COLOR, AGE, SEX	SYMPTOMS AND THEIR DURATION	PHYSICAL SIGNS	MUR-MUR AUDIBLE TO PATIENT	BLOOD PRESSURE	WASSER-MANN REACTION	INTERVAL BETWEEN RECURRENCES OF MURMUR AND FINAL OUTCOME	FINAL OUTCOME	NECROPSY FINDINGS OR CLINICAL DIAGNOSIS
1	B., 39, M.	Dyspnea on exertion; substernal pain; cough in chest; (6 wk.)	Loud, musical, diastolic murmur (and thrill).	yes	150/55	+	10 wk.	Died with bronchopneumonia	Necropsy diagnosis: Syphilitic aortitis with aortic insufficiency, eversion of the right anterior leaflet.
2	W., 43, M.	Dyspnea at rest; edema; (3 mo.)	Loud, humming, diastolic murmur (and thrill); signs of congestive failure.	no	148/20	+	4 wk.	Died suddenly.	Necropsy diagnosis: Syphilitic aortitis with aortic insufficiency, eversion of the right anterior leaflet.
3	B., 50, M.	Dyspnea at rest; edema; precordial pain. (6 mo.) (Evidence of paresis.)	Loud, musical diastolic murmur (and thrill); signs of congestive failure.	no	170/80	+	1 wk.	Died with congestive failure.	Necropsy diagnosis: Syphilitic aortitis with aortic insufficiency, eversion of the right anterior leaflet.
4	B., 40, M.	Dyspnea at rest; edema; (1 yr.)	Loud, musical diastolic murmur (and thrill); evidences of congestive failure.	no	170/80	neg.	5 mo.	Died with congestive failure.	Necropsy diagnosis: Syphilitic aortitis with aortic insufficiency, eversion of the right anterior leaflet.
5	B., 35, F.	Orthopnea; anasarca. (1 yr.)	Loud, musical, diastolic murmur (and thrill); signs of marked congestion.	no	170/20	neg.	3 wk.	Died with congestive failure.	Necropsy diagnosis: Syphilitic aortitis with insufficiency, eversion of the right anterior and posterior leaflets.

of retroverted leaflets parallel to the free margin; he suggested that this might produce eversion by acting in a sense as a fulcrum, over which the free edge of the leaflet, distal to the fibrous band, might be bent backward toward the left ventricular cavity by the regurgitant column of blood. In some of our cases there was such a dense fibrous band. In others, although the band was present, it was not dense or tight and looked as if it might have been caused by a heaping up or wrinkling of the endocardium which developed secondary to, and not preceding, the retroversion. Other examples, notably in the two cases in which the leaflets were studied histologically (Fig. 3), showed no trace of a longitudinal fibrous band.

We wish to suggest another possible factor that may contribute to retroversion, namely, loss of the support normally furnished by the elastica. In normal aortic valve leaflets, the elastica can be traced in an unbroken line from the upper part of the left ventricle almost to the free margin of the leaflets. It lines the entire undersurface of the leaflet and is firmly attached at the commissures, thus forming a sort of sling which supports the leaflets and probably aids in maintaining their normal shape and contour. In the unverted syphilitic valves that we have seen histologically, the elastica was still largely intact (Fig. 4); in the two retroverted leaflets studied histologically, the elastica was entirely absent (Fig. 3). Since we have studied only two retroverted leaflets histologically, we, of course, cannot say that the elastica is always destroyed in retroverted leaflets. We can say that it may be, and that, when it is absent, a leaflet will have lost one of the structures that probably aids in maintaining its normal structure.

We do not wish to draw any conclusions as to the mechanism of retroversion from such meager material, except to say that it seems not unlikely that a number of factors may contribute. We have introduced this somewhat hypothetical discussion mainly to point out the destruction of the elastica in the two cases studied histologically.

SUMMARY AND CONCLUSIONS

1. The diastolic murmur of aortic insufficiency may have a strikingly musical quality and may be quite loud. The report of a series of eleven patients* with such unusual murmurs is presented and discussed.

2. In the six patients who came to necropsy, syphilis was the cause of the aortic insufficiency. In five of the remaining patients, the clinical etiologic diagnosis was also syphilis. In one patient, a boy 11 years of age, the etiology was rheumatic fever.

3. Retroversion of the right anterior aortic valve leaflet, rather than the usually assigned cause, i.e., rupture or tear of an aortic

*Since the original series of 11 patients was collected, 3 additional patients presenting loud, musical, diastolic murmurs have been studied both clinically and at necropsy. All three showed syphilitic aortic insufficiency with retroversion of the right anterior valve leaflet.

leaflet, is emphasized as the commonest cause of loud, musical, aortic diastolic murmurs. This lesion, first suggested as a cause by Hodgkin, in 1829, was present in the six patients of our series who came to necropsy.*

4. The mechanism by which retroversion is produced is discussed.

We wish to express our great appreciation to the chiefs upon whose services these patients were studied, and to the pathologists who performed the necropsies, for permission to report these observations.

REFERENCES

1. Hodgkin, T.: On Retroversion of the Valve of the Aorta, *London Med. Gazette* 3: 433, 1829.
2. Scott, R. W.: Disease of the Aorta, In *Oxford Medicine*, Vol. 2, Part 2, p. 508, New York, Oxford University Press.
3. Howard, C. P.: Aortic Insufficiency Due to Rupture by Strain of a Normal Aortic Valve, *Canadian M. A. J.* 19: 17, 1928.
4. Elliotson, J.: *Diseases of the Heart*, London, 1830, Longman, Rees, Orme, Brown and Green.
5. Bertin, Par. R. J.: *Traite des Maladies du Cœur et des gros Vaisseaux*, Paris, 1824, Chez, J. B. Bailliere, Libraire.
6. Hope, J.: *Diseases of the Heart and Great Vessels*, Philadelphia, 1842, Lea and Blanchard.
7. Peacock: Case of Diseased Heart in Which a Musical Murmur Was Heard During Life, *Trans. Path. Soc. Lond.* 6: 55, 1854.
8. Stokes, W.: *Diseases of the Heart and Aorta*, Philadelphia, 1855, Lindsay and Blakiston, p. 139.
9. Wunderlich, C. A.: *Handbuch der Pathologie und Therapie*, Vol. 3, 1855, p. 557, Stuttgart, Ebner.
10. Banks, J. T.: Perforation of the Aortic Valves—Loud Musical Murmur, *Dublin Hosp. Gazette* 14: 33, 1857.
11. Wilson, F. N., and Jamieson, R. A.: The Musical Murmur of Aortic Insufficiency, *Heart* 7: 1918-1920.

*See footnote on page 492.

Department of Clinical Reports

QUINIDINE IN THE TREATMENT OF BENIGN AURICULAR FIBRILLATION WITH REPEATED EMBOLI*

REPORT OF A CASE

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THE indications and contraindications for the use of quinidine in auricular fibrillation have been subjected to several changes since the drug was first introduced, in 1918. The present position is perhaps most representatively stated by White,¹ who considers the patient with auricular fibrillation a possible candidate for quinidine therapy if he has no congestive failure, serious heart disease, or history of embolism. Kerr² adds that the drug should not be used if the underlying condition is such that restoration of normal rhythm would not improve the condition of the patient.

Recently, we have had a patient with chronic auricular fibrillation of uncertain etiology, whose only symptoms were those of repeated emboli. The question arose whether quinidine should be used to convert the rhythm to normal, with the idea of preventing subsequent emboli. The chances of a subsequent disabling or fatal embolus with the conservative treatment which was being employed were weighed against the chances entailed in the conversion to normal rhythm with quinidine. Three emboli in the systemic circuit had occurred within five weeks, two of them when the patient was at rest in bed, with no evidence of cardiac failure, and with a well-controlled ventricular rate (digitalis). It was, therefore, deemed justifiable to attempt to eliminate the auricular fibrillation.

A review of the literature was made to evaluate the risk of quinidine therapy. It is fairly well established that the drug restores normal mechanism in about 60 to 65 per cent of the cases (Wolff and White,³ Campbell and Gordon,⁴ Fahr⁵), and that the probabilities of success are greater in individuals with auricular fibrillation of short duration and little evidence of organic cardiac disease (Wolff and White,³ Campbell and Gordon⁴). The degree of risk involved in attempting to convert the rhythm is not universally agreed upon, since this is likely to be interpreted in terms of the untoward results in one's own

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*Aided by the A. D. Nast Fund for Cardiac Research.

Received for publication April 7, 1939.

experience. The early reports dealing with quinidine (Herrmann and Wilson⁶) emphasized the danger of embolism when the drug was used in auricular fibrillation. However, subsequent studies (Viko, Marvin, and White,⁸ Parkinson and Campbell,⁹ Levy,¹⁰ Cookson¹¹) showed that embolic accidents were no more frequent with quinidine than with digitalis therapy. Fahr⁵ states that the risk of embolism has been distinctly overemphasized. Apparently the frequency of such accidents, as well as sudden death, in the natural history of this arrhythmia has not been fully appreciated. Emboli do occasionally occur after quinidine therapy, and the chronologic relationship suggests the possibility of cause and effect. In many cases, however, the relationship is not clear.

The importance to be attached to previous emboli as a possible contraindication to quinidine therapy has not been sufficiently evaluated. It is usually stated that such an occurrence is a contraindication. However, there has been no clear evidence to show that the frequency of emboli following quinidine therapy is greater in patients with a history of embolism. Instances in which quinidine was given without mishap to patients who previously had shown embolic phenomena are cited by Clark-Kennedy,¹² Oppenheimer,¹³ Campbell and Gordon,⁴ and Parkinson and Campbell.⁹ The last-named authors were successful in restoring normal mechanism in a patient who had mitral stenosis, a large heart, and auricular fibrillation of five years' duration, and had had three hemiplegic episodes within the preceding two years. Five years later the patient was well and vigorous, with a sinus rhythm. They point out that the return to sinus rhythm may prevent the circumstances which lead to the formation of auricular thrombi.

More important than the risk of embolism is the toxic action of quinidine on the myocardium. Sudden death has been reported with the use of the drug, but only rarely has the cause been embolic (Hay,⁷ Viko, et al.,⁸ Parkinson and Campbell⁹). Korns¹⁴ found that experimental quinidine poisoning resulted in death due to ventricular fibrillation in dogs, and to standstill of the entire heart in guinea pigs. Kerr,¹⁵ and also Davis and Sprague,¹⁶ have described ventricular fibrillation in patients following the use of quinidine. Wolff and White³ noted auricular standstill, with a shift of the pacemaker to the A-V node, in two patients after quinidine administration. Since the ventricle is also depressed by quinidine, they suggested that cardiac standstill may have been the cause of some of the reported cases of sudden death. However, we have not been able to find any instance in which this was proved. Clark-Kennedy¹² noted the appearance of new cardiac symptoms or the aggravation of already existing ones in seven out of eight cases in which quinidine failed to restore normal rhythm. The fact that the few autopsies which have been performed in the cases of sudden death have rarely disclosed the cause of death favors

the view that ventricular fibrillation or cardiac standstill may have been responsible. There is also the possibility of respiratory paralysis, which is the cause of death in cats (Gordon, Matton and Levine¹⁷).

Analysis of the literature indicates that the most serious risk with quinidine therapy is the myocardial toxicity of the drug, and that the danger of embolism, while real, has been overemphasized. The danger of serious myocardial poisoning in our patient was small, since he had no evidence of cardiac embarrassment and only slight enlargement of the heart.

The risk of forming emboli seemed to be but slightly greater than that already present; thus we felt that quinidine could be used provided careful clinical and electrocardiographic control was observed during the treatment. The drug was given to restore normal rhythm and to eliminate the underlying factors which favored the formation of auricular thrombi. This was done successfully; normal sinus rhythm was restored and maintained. No further emboli have occurred in eight months.

CASE REPORT

The patient, a 49-year-old, white, married tailor, entered the Michael Reese Hospital on the service of Dr. Sidney Portis, June 29, 1938, with acute embolism of the right brachial artery of forty-eight hours' duration. He had suddenly developed pain in the center of the antecubital fossa, which had gradually increased in intensity and had been followed by coldness and cyanosis of the forearm.

The patient first discovered that he had heart disease six years earlier, when a physician whom he consulted for an incidental complaint told him that his heart was irregular. During these years, the patient was seen twice on the surgical service, and both times auricular fibrillation was noted. There was a history of two episodes in the preceding three years which may have been embolic in nature. The first was characterized by sudden numbness, weakness, and paresthesias of both feet, especially the right, lasting thirty minutes. The second occurred a year before admission and was characterized by sudden dimness of vision, lasting ten minutes. Aside from these, the patient has had no symptoms of any nature which might be related to the cardiovascular system. He gave no history of rheumatic fever, hypertension, thyrotoxicosis, syphilis, or nephritis.

On examination, the patient was of sthenic build, had an anxious expression, and complained of pain, coldness, and numbness in the upper right forearm. The only positive findings were those related to the embolus and to the cardiovascular system. Ophthalmoscopic examination showed arteriosclerotic vessels. There were no signs suggesting hyperthyroidism. The lungs were completely negative. A faint systolic murmur was heard both at the apex and base, loudest at the apex. No cardiac enlargement could be detected, and no diastolic murmurs were heard. The heartbeat was grossly irregular, with a ventricular rate of 110 per minute and a pulse deficit of 30. The blood pressure in the left arm was 130/80. Neither the liver nor spleen was palpable. The lower extremities showed no edema, cyanosis, or clubbing. There were no petechiae.

The right arm showed slight swelling and tenderness just below the bifurcation of the brachial artery, and the right forearm was cold and blue. The right radial pulse was not palpable.

Dr. S. Perlow found that both popliteal pulses were but faintly palpable, and that neither the dorsalis pedis nor the posterior tibial pulse could be felt in either leg. Buerger's test was negative in both legs. The oscillometric indices were normal for both thighs, but were diminished in both legs.

The urine was normal, and there was no anemia. The serologic reactions were negative. The nonprotein nitrogen and sugar content of the blood were normal, as was the basal metabolic rate. Repeated agglutination tests and three blood cultures were negative.

A roentgenogram of the chest showed a slightly enlarged left ventricular shadow, with a contour of the aortic type. The cardiothoracic ratio was $\frac{17.7}{35.0}$ cm. The lungs were negative. Fluoroscopic examination confirmed these findings and showed no enlargement of the pulmonary conus or the left auricle in the oblique views. The esophagus was not displaced.

The electrocardiogram showed auricular fibrillation with a ventricular rate of 100, left axis deviation, ventricular extrasystoles, an upright T_1 and T_2 , and a small, inverted T_3 . The chest leads were normal.

The diagnosis rested between coronary sclerosis and rheumatic heart disease with mitral insufficiency or aortic stenosis. The sclerotic changes in the retina and in the lower extremities seemed to favor the former.

The patient was put to bed and treated with papaverine; digitalis was used to slow the ventricular rate. The arm gradually improved, the tenderness lessened, and the color became more normal, but weakness of the grip persisted. A week after entry (July 9) he was awakened by sudden pain in the right thigh, with numbness and coldness of the foot. The pulsation in the right femoral artery was markedly diminished, and the foot was cold and blue; it was thought that he had a small femoral embolus. These symptoms gradually abated, the femoral pulse returned to normal in a few days, and the patient was apparently doing well. A month later (August 8) he developed identical symptoms and signs on the left side. These also subsided uneventfully, but the left femoral pulse only partially returned to normal.

It was at this time that we decided to use quinidine. The ventricular rate was 70 per minute, and the maintenance dose of digitalis was continued. After a test dose of quinidine to rule out idiosyncrasy to the drug, the dose was gradually increased until he received 0.4 gm. every four hours, day and night. On the second day on this dose, after a total of 12.0 gm. had been given, sinus rhythm returned (Aug. 25). He was kept in bed for three days, and the dose of quinidine was gradually reduced to 0.2 gm. four times a day, for maintenance.

Following the restoration of the normal rhythm, the faint systolic murmur previously noted became much louder and harsher, but no diastolic component could be heard. Teleoroentgenograms showed that the heart was smaller and normal in size and contour. The cardiothoracic ratio at this time was $\frac{15.2}{33.0}$ cm. No significant

changes in blood pressure were noted. The electrocardiogram showed sinus rhythm with a P-R interval of 0.20 sec. and a rate of 64 per minute. The left axis deviation previously seen was no longer present. $S-T_1$ and $S-T_2$ were slightly depressed, and $S-T_3$ (CF_4) was depressed. The T waves were upright in all leads. It was thought that these changes may have been due to quinidine.

Since leaving the hospital, the patient has been seen frequently by his physician (Dr. S. Perlow), who reports that he has remained well; he has had no symptoms of cardiac embarrassment and no further emboli. An electrocardiogram taken in March, 1939, showed sinus rhythm.

The patient re-entered the hospital in May, 1939, with fever, dyspnea, and weakness. Paroxysmal auricular fibrillation developed shortly after entry, but this was

abolished by increasing the dose of quinidine to 0.4 gm. four times a day. He died a week later, before a definite diagnosis had been made. Permission for an autopsy could not be obtained.

DISCUSSION

The striking feature of the case was the fact that over a period of at least six years, during which auricular fibrillation was known to have been present, the only manifestations of cardiovascular disease, other than the arrhythmia (of which the patient was unaware), were repeated emboli. At least three, and possibly five, embolic accidents had occurred within the three years prior to entry; three occurred within five weeks of observation. Following the third embolus, it was felt that subsequent emboli, one of which might be serious or fatal, were not unlikely. A careful review of the literature suggested that the major risk in the use of quinidine was the direct myocardial toxicity of the drug, which was responsible for most of the reported fatal accidents, and that the incidence of emboli with quinidine was no greater than might be expected with conservative digitalis therapy. The absence of synergic auricular contractions appeared to be the underlying mechanism responsible for the formation of mural auricular thrombi. The frequency and widespread distribution of the emboli made it advisable to abolish the conditions favoring thrombus formation, if possible, more especially because the prognosis was otherwise very good. After weighing the risks, quinidine therapy was instituted and normal rhythm restored. The subsequent course has been satisfactory in that sinus rhythm has been maintained up to the present (eight months), no further emboli have occurred, and the cardiac state has continued excellent.

Our experience in this case suggests that when a patient has auricular fibrillation, repeated emboli, and a good myocardial function and life expectancy, serious consideration should be given to the possibility that quinidine may re-establish normal auricular activity and diminish the likelihood of further emboli. If the hazard when untreated is considerable, and the benefits to be gained are many, the therapeutic risk may be justifiably taken.

SUMMARY

Quinidine sulfate was given to a middle-aged man with "benign" auricular fibrillation of uncertain etiology whose repeated emboli were the only manifestations of his disease. The result was satisfactory, with restoration of sinus rhythm, subsidence of embolic phenomena, and maintenance of excellent cardiac reserve. The risks and benefits of the use of quinidine in such cases are discussed.

The author is grateful to Dr. L. N. Katz for suggestions during the study and in the preparation of the report.

REFERENCES

1. White, P. D.: Heart Disease. New York, 1937, Macmillan Co.
2. Kerr, W. J.: The Use of Quinidine in the Treatment of Cardiac Irregularities. The Cyclopedia of Medicine, Philadelphia, 1934, F. A. Davis Co.
3. Wolff, L., and White, P. D.: Auricular Fibrillation. Results of Seven Years' Experience with Quinidine Sulfate Therapy, Arch. Int. Med. 43: 653, 1929.
4. Campbell, M., and Gordon, F. W.: The Quinidine Treatment of Auricular Fibrillation, Quart. J. Med. 5: 205, 1936.
5. Fahr, G.: The Treatment of Cardiac Irregularities, J. A. M. A. 111: 2268, 1938.
6. Wilson, F., and Herrmann, G. R.: Cerebral Embolism Following the Arrest of Auricular Fibrillation by Quinidine, J. A. M. A. 78: 865, 1922.
7. Hay, J.: The Action of Quinidine in the Treatment of Heart Disease, Lancet 2: 543, 1924.
8. Viko, L. E., Marvin, H. M., and White, P. D.: A Clinical Report on Quinidine Sulfate, Arch. Int. Med. 31: 345, 1923.
9. Parkinson, J., and Campbell, M.: Quinidine Treatment of Auricular Fibrillation, Quart. J. Med. 22: 281, 1929.
10. Levy, R. L.: The Clinical Toxicology of Quinidine, J. A. M. A. 78: 1919, 1922.
11. Cookson, H.: The Etiology and Prognosis of Auricular Fibrillation, Quart. J. Med. 23: 309, 1930.
12. Clark-Kennedy, A.: Quinidine in the Treatment of Auricular Fibrillation, Quart. J. Med. 16: 204, 1922.
13. Oppenheimer, B. S., and Mann, H.: Results with Quinidine in Heart Disease, J. A. M. A. 78: 1752, 1922.
14. Korns, H. M.: An Experimental and Clinical Study of Quinidine Sulphate: I, Experimental, Arch. Int. Med. 31: 15, 1923.
15. Kerr, W. J., and Bender, W. L.: Paroxysmal Ventricular Fibrillation with Cardiac Recovery in Case of Auricular Fibrillation and Complete Block under Quinidine Sulfate Therapy, Heart 9: 269, 1922.
16. Davis, D., and Sprague, H. B.: Ventricular Fibrillation: Its Relation to Heart Block, AM. HEART J. 4: 559, 1929.
17. Gordon, B., Matton, M., and Levine, S. A.: Mechanism of Death from Quinidine and a Method of Resuscitation; An Experimental Study, J. Clin. Invest. 1: 497, 1925.

SUBACUTE BACTERIAL ENDOCARDITIS CAUSED BY THE TYPE XVIII PNEUMOCOCCUS

REPORT OF A CASE

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KINGSTON, N. Y.

IN ACUTE streptococcus endocarditis the infection of the heart valves is usually only incident to a general beta-hemolytic *Streptococcus* septicemia, associated with a recognizable extracardiac source of infection, such as wounds, mastoiditis, sinus thrombosis. *Streptococcus viridans* endocarditis, on the other hand, is primarily a valvulitis with thrombus formation superimposed on a previously damaged valve, and with the portal of entry of the bacteria into the body obscure or exceedingly questionable.

Libman has observed in his series of cases of subacute bacterial endocarditis that the *Streptococcus viridans* was the cause in 95 per cent, and the influenza bacillus in the other 5 per cent. Various students of this type of endocarditis have reported other causative organisms, but I have been unable to find any reports stating that the pneumococcus might be the etiologic agent in this slowly progressing and fatal disease. The following case report proves conclusively that the type XVIII pneumococcus may give rise to subacute bacterial endocarditis with clinical and pathologic manifestations which are indistinguishable from those observed in *Streptococcus viridans* endocarditis.

CASE REPORT

M. M., a 6-year-old white girl, had been a healthy child until she reached the age of three years, when, following a mild tonsillitis, she developed "heart trouble." For three years she had experienced dyspnea when climbing stairs, and one year previously a mitral systolic murmur had been discovered. On Jan. 23, 1939, she was seen the first time by her physician. The child had mild tonsillitis, with a temperature of 101.4° F. Other members of the family were suffering from hemolytic streptococcus throat infections at the time, so that no culture was made from her throat. Sulfanilamide was given, and after two days she was feeling as well as usual and was out of bed. A few days later she was found to have a fever ranging between 101° and 103° F., and on Jan. 30, 1939, she was admitted to the Kingston Hospital.

Upon admission the patient had no complaints but was pale and listless and had a "café au lait" discoloration of the skin. The tonsils were large and free of signs of inflammation. The mucous membranes were pale, and no petechiae could be found in them or in the skin or eye grounds. There was no clubbing of the fingers. The lungs were clear throughout. The heart was not enlarged. A low-pitched systolic murmur could be heard at the apex and was transmitted to the axilla. There was some accentuation of the pulmonic second sound, but no other alterations could be detected. The pulse was regular and of good quality, and the rate was 100. The blood pressure was 80/50. The liver and spleen could not be palpated, and nothing of significance could be found in the abdomen or extremities.

Laboratory examinations revealed that the erythrocyte count was 3,840,000 and the hemoglobin 69 per cent (16.5 gm. = 100 per cent). There were 15,800 leucocytes per cu. mm., 83 per cent of which were polymorphonuclears. Slight albuminuria was present, but no erythrocytes could be found in the urinary sediment. The complement-fixation test for syphilis was negative. Roentgenologic studies revealed no disease processes in the mastoids. A teleoroentgenogram showed no increase in the size of the cardiac shadow.

Sulfapyridine was administered. After eight doses of 0.5 gram each, persistent vomiting developed, and a marked agranulocytosis was noted. The child received numerous blood transfusions. Neoprontylin therapy was attempted, but after a few small doses toxic symptoms again supervened, which necessitated the discontinuance of the treatment. The temperature ranged from 99.4 to 101° F. Daily urine examinations revealed occasionally a few erythrocytes and leucocytes. Blood cultures on six occasions were all positive for the type XVIII pneumococcus.

The organisms were isolated from the blood after 48 hours' incubation at 37° C. and grew in the pour plates with the formation of a wide zone of methemoglobin, and the organisms in the broth culture grew out in chains ranging from 6 to 200 members in length. The bacteriologic picture presented resembled that usually shown by the *Streptococcus viridans*. However, as is usual with organisms producing alpha hemolysis, the culture was examined serologically with the various antipneumococcic sera and tested for bile solubility and for ability to ferment inulin. The serologic reactions immediately classed this organism as a type XVIII pneumococcus.

On Feb. 10, 1939, the patient complained of pain in the lower part of the left side of the chest on inspiration, and at this time the spleen and liver were palpable. A few isolated petechiae were noted on the abdominal wall and lower extremities. The asthenia and lassitude became progressively more marked. On March 3, 1939, complete right-sided hemiplegia was noted, coma ensued, and the child died on March 10, 1939.

Final Clinical Diagnoses.—(1) Healed rheumatic mitral endocarditis with superimposed subacute bacterial endocarditis caused by the type XVIII pneumococcus; (2) splenic infarction; (3) right-sided hemiplegia; and (4) focal, embolic glomerulitis.

Necropsy Findings.—The heart, which was slightly enlarged, was found to be the seat of a healing rheumatic endocarditis and myocarditis. There were many recent perivascular scars in the muscle, and marked thickening of the leaflets of the mitral valve and thickening and shortening of the chordae tendineae. Small fibrous vegetations were present along the auricular aspect of the edges of both the mitral and tricuspid valves. Protruding into the auricle, and practically filling the mitral orifice, was a large, firm, friable vegetation attached to the aortic leaflet of this valve. Direct typing of the large number of cocci present by the Neufeld method revealed that these organisms were type XVIII pneumococci. Cultures of the vegetation yielded a pure growth of this pneumococcus. Extensive embolic manifestations were present. These included multiple petechiae in the skin, multiple recent and old yellow infarcts in a markedly enlarged spleen, and multiple petechiae in both kidneys, which showed, microscopically, changes characteristic of embolic nephritis.

Microscopic examination of the large vegetation on the mitral leaflet showed old thrombus material at the point of attachment to the valve, which was undergoing organization with the ingrowth of blood vessels and fibroblasts. Toward the center of the thrombus it was necrotic and contained no bacteria. Recent thrombus was present near the surface, and huge quantities of bacteria lay along the zone between the recent and necrotic thrombus material. A thin film of fresh blood clot, probably post-mortem clot, covered most of the surface of this large

vegetation. Partial destruction of the valve had occurred, and in that portion which remained there was a subacute inflammation. The cells present in the original portion of valve were chiefly mononuclears, with a few polymorphonuclear leucocytes scattered throughout this tissue. The changes observed in the valve and vegetation suggested that the bacterial endocarditis had long antedated the onset of clinical signs and symptoms.



Fig. 1.—Large vegetation on auricular aspect of aortic leaflet of mitral valve.

COMMENT

In this case of subacute bacterial endocarditis caused by the type XVIII pneumococcus the *Streptococcus viridans* would in all probability have been regarded as the causative organism had not the more recently available serologic methods for distinguishing higher types of pneumococci been employed. It is therefore imperative that in every case of subacute bacterial endocarditis the organism be subjected to serologic studies to make sure that it is not a pneumococcus. The Neufeld reaction in particular, should be employed. If this were done it is highly probable that many cases such as that herein reported would be discovered.

I wish to express my gratitude to Mr. George C. Groves for his aid in the isolation and identification of the type XVIII pneumococcus in this case.

Department of Reviews and Abstracts

Selected Abstracts

Sprenger, O.: Abstract of Meeting of Twelfth German Society of the Study of the Circulation. *Ztschr. f. Kreislaufforsch.* 31: 312, 1939.

E. Schütz (Münster) pointed out that the S-T deviation in the electrocardiogram is an expression of monophasic action currents from injured areas superimposed on ordinary action currents.

A. Weber (Bad-Nauheim) emphasized that the electrocardiogram gives no information concerning the mechanical activity of the heart, but shows evidence of local myocardial injury and alterations in spread of impulse. S-T deviations are symptoms, like dyspnea, but point to coronary insufficiency whether these are accompanied by infarction or not.

• Büchner (Freiburg) was in accord in stating that necrosis is a late occurrence of coronary insufficiency of which the electrocardiographic changes are earlier evidence.

K. Heinrich (Bad-Nauheim) reported that the injury current potential in the frog's heart is smaller than the action current potential.

Hegglin and Nobile (Zurich) reported that in the mammalian heart warming, calcium, and digitalis shorten the monophasic curve, while hypocalcemia and quinine lengthen it. They differentiated between lengthening of the sustained plateau and decline of the monophasic curve. The former indicates a protraction of the state of maximum activation, the latter slow restitution.

Holzman (Zurich) spoke about middle wall infarction, which in the chest lead, with the electrode over the left sternum, shows the QRS entirely inverted; but with the electrode over the apex, shows a normal QRS but an inverted, peaked T.

G. Kayser and G. Unger (Bad-Nauheim) reported that mirror oscillographs instead of cathode ray oscillographs could be used in vector diagraphy.

Ter Borgh (Utrecht) reported anatomic studies in the horse and beef where injection showed that there were extensive connections in the septum between the right and left bundles, and that the Purkinje net extended into the myocardium as far as the epicardium.

Jung and Jantz (Freiburg) noted a prolongation of electrical systole unrelated to rate when potassium increases in blood as a result of paralysis. This disappears when the attack is over or when calcium is added.

A. V. Allen (Rochester, Minn., U. S. A.) spoke on sympathectomy in the treatment of hypertension.

Hildebrand (Frankfurt) found that a salt-free diet led to subjective improvement in only one-third of twenty-seven patients with hypertension upon whom this was tried.

M. Hochrein (Leipzig) considered hypertension to be divisible into an early and late stage. Since aging of arteries is accelerated by hypertension, lowering of blood pressure in the early stage is indicated. In the late stage the problem centers about the handling of the heart.

Sarre and Wirtz (Frankfurt) reported that denervation had no effect on the kidney flow or the A-V O₂ difference of animals with experimental diffuse glomerulonephritis.

Broemser (Munich) discussed the physiology of heart failure in terms of the abnormal states of elasticity and resistance of the blood vessels and in terms of the circulating blood volume and the state of the venous circulation.

H. Gremels (Marburg)—Heart failure is due to insufficiency of energetics. Treatment can be attempted by mobilization of energy via the sympathetics or to increase its build up by vagus-insulin stimulation. Digitalis appears to cause a decreased membrane permeability of heart muscle and an increased effectiveness of normal vagus stimulation.

F. Volhard (Bad-Nauheim) presented his views on digitalis and strophanthin, namely that they decrease diastolic volume of failing heart and thus lead to increased mechanical work and efficiency. Strophanthin also increases peripheral O_2 utilization. Rest is important in heart failure and venesection is occasionally useful, as are leeches. Mercurial diuretics should be used after heart muscle has been strengthened. Dietary regime aiming to relieve edema is to be used. Starvation is advocated as a cure for high blood pressure, to be followed by absolute salt-free diet. Focal infection of tonsils should be eradicated. In certain cases, thyroidectomy is useful.

Blumberger (Düsseldorf) measured isometric contractions and ejection period of systole and advocated their use in estimating myocardial damage.

Schellong (Heidelberg) presented the changes which occur during ordinary and deep breathing in the electrovector diagram.

Parade (Breslau) reported that digitalis causes a decrease of the alkali curve after exercise, indicating that it produces an improved lactic acid synthesis in the muscles and liver.

Eckardt (Hamburg) noted that not all of early changes in circulation in diphtheria is due to vascular failure since severe damage to the heart is found in the earliest stages of diphtheria as could be demonstrated anatomically.

KATZ.

Scupham, George W., de Takats, Geza, VanDellen, Theodore R., and Beck, William C.: Vascular Diseases: A Review of Some of the Recent Literature, With a Critical Review of the Surgical Treatment. Arch. Int. Med. 64: 590, 1939.

This annual review of recent literature on vascular diseases is one similar to the one on heart disease. They are both invaluable résumés of their particular subjects.

McCULLOCH.

Comroe, Julius H., Jr.: The Location and Function of the Chemoreceptors of the Aorta. Am. J. Physiol. 127: 176, 1939.

The extracarotid chemoreceptors of the dog have been localized by physiologic and anatomic studies in the *aortic body*, a structure fundamentally similar to the carotid body.

Both carotid and aortic bodies set up reflexes to the respiratory and vasomotor centers in response to anoxia, whether this be produced systemically by oxygen lack in the inspired air, or locally by interference with tissue oxidations.

The major role of the aortic chemoreceptors in the dog is the initiation of powerful reflexes to the vasomotor center during anoxemia. By far the greater portion of the hypertension of acute systemic anoxia is produced by aortic body reflexes; vascular reflexes from the carotid body are inconstant and relatively ineffective. The carotid body, however, usually contributes by far the greater portion of the hyperpnea of anoxemia in the dog; the aortic body component,

though invariably present, is often insignificant. In the cat the carotid chemoreceptors are relatively more important to the vasomotor response to anoxia than is the case in the dog.

The blood supply and afferent nervous pathways for the aortic chemoreceptors have been determined in the dog and cat. In the dog the blood supply is from the transverse aorta, in the cat from the coronary arteries. In both species the nerve fibers reach the vagus trunk close to (probably by way of) the recurrent laryngeal nerves.

The possibility that the McDowall reflex may result from chemical stimulation of the aortic body rather than from alterations in venous pressure has been discussed.

In view of the close functional and structural similarity to the carotid body, it is proper to use the term *aortic body* suggested by Nonidez, to designate structures now known as *paraganglion aorticum supracardiale*, *paraganglion of Penitschka*, *paraganglion aorticum supracardiale superius*.

AUTHOR.

Smith, Paul K., Winkler, Alexander W., and Hoff, Hebbel E.: Calcium and Digitalis Synergism. Arch. Int. Med. 64: 322, 1939.

Dilute solution of calcium chloride was administered intravenously to digitalized dogs, and electrocardiograms and samples of blood were taken frequently during the course of the injection.

The electrocardiographic changes were correlated with the concentration of calcium in the serum. They were similar in every way to those of normal animals receiving calcium.

The mode of death of the digitalized animals was by ventricular fibrillation, or by arrest without fibrillation, just as in normal animals.

A comparison of the fatal dose and of the concentration of calcium in the serum at death in normal and digitalized dogs indicated that, by the type of experiment described here, the lethal effects of calcium and digitalis are neither synergistic nor even completely additive.

AUTHORS.

Keys, Ancel, and Friedell, H. L.: Measurement of the Stroke Volume of the Human Heart From Roentgenograms; Simultaneous Roentgenkymographic and Acetylene Rebreathing Experiments. Am. J. Physiol. 126: 741, 1939.

A method is described in which the volume stroke of the human heart is estimated from measurements of the areas of the systolic and diastolic outlines of the heart in the frontal position on a roentgenkymographic film.

Roentgenkymograms were made simultaneously with acetylene rebreathing experiments. The results from twenty-five experiments on sixteen normal subjects fit the equation:

$$\text{Stroke volume} = 0.64 \left(\text{Area}_{\text{diastole}}^{1.45} - \text{Area}_{\text{systole}}^{1.45} \right).$$

The average difference between the two methods was ± 5.1 per cent and the greatest differences were $+10.7$ and -10.2 per cent, referred to the acetylene method as standard. Similar results were obtained with patients with circulatory abnormalities (myxedema, nephritis, hypertension) so long as no valvular defects were present.

Patients with valvular leaks (mitral insufficiency, aortic regurgitation) always have stroke volumes, measured by the kymograph, which are larger than the true stroke volume and this discrepancy is parallel to the best judgment of the leak

Since peripheral arteriosclerotic disease involves the lower extremities to a much greater extent than it does the upper, oscillometric readings at any given level in the lower extremities should, as the disease progresses, decrease proportionately more than those at any given level in the upper extremities.

The ratio of the amplitude of pulsation at the ankle to that at the wrist was between 1 and 2 in normal individuals. In patients with peripheral arteriosclerotic disease this ratio was always under one.

NAIDE.

Castex, M. R., Arana, R., Ramirez, R. L., and Battro, A.: Paroxysmal Ventricular Tachycardia. *Rev. argent. de cardiol.* 5: 365, 1939.

Seven cases are described of paroxysmal ventricular tachycardia with EKG records obtained during the attacks. In cases 1, 2, and 3, these were due to occlusion of the right coronary, and in case 4, to occlusion of the left one. The ventricular complex was positive in the former and negative in the latter (Lead I).

Assuming that the left coronary occlusion causes a focus of hyperirritability in the affected area or its vicinity on the anterior wall of the ventricle, apex, and anterior part of the septum, the extrasystoles, isolated or in groups, thus originated, would cause the ventricular tachycardia. According to this interpretation, ventricular complexes with initial deflexion in Lead I would originate in the right ventricle, or posterior wall of the left one, and those with negative deflexion, in the left ventricle, which is in agreement with the conclusions of Barker, Macleod, and Alexander, regarding the origin of the extrasystoles.

With the exception of case 2, the observations reported did not correspond to septal infarcts and therefore are in disagreement with the hypothesis that ventricular paroxysmal tachycardia is always the expression of a septal infarct. Pathologic examinations are needed to elucidate the question.

Of the remaining three cases one belonged to a syndrome of Stokes-Adams produced by paroxysmal ventricular tachycardia, the other to a tachycardia of Bouveret which later on degenerated to a prefibrillar tachycardia, and the third was interpreted as being ventricular tachycardia.

AUTHORS.

Perry, C. Bruce: Persistent Conduction Defects Following Diphtheria. *Brit. Heart J.* 1: 117, 1939.

A description has been given of three children who recovered from attacks of diphtheria with persistent conduction defects. In two this took the form of complete heart block, and in the third of bundle branch block. In all three the lesion seems to have developed at the time of their diphtheria or shortly after, and in all it has persisted for some years.

AUTHOR.

Campbell, Maurice, and Elliot, G. A.: Paroxysmal Tachycardia; Etiology and Prognosis of One Hundred Cases. *Brit. Heart J.* 1: 123, 1939.

One hundred unselected cases of paroxysmal tachycardia have been studied and followed for some years. In forty-two the diagnosis was confirmed by the electrocardiograph, in thirty by observation of an attack, and in twenty-eight by the history alone. The criteria of diagnosis, when this has to be made on history, have been described, the sudden onset of palpitation being the most reliable single symptom. There may sometimes be difficulty in distinguishing paroxysmal flutter and tachycardia.

Of the forty-two attacks with graphic records, eight were ventricular and thirty-four supraventricular; eleven of the latter were nodal, but in many of the other twenty-three the site of origin could not be defined more precisely. Extrasystoles were observed between attacks in twenty-one but were only of minor assistance in predicting the type of the attack. Ventricular paroxysms were very uncommon without serious heart disease.

There were forty-one of these cases with heart disease, nineteen rheumatic, two syphilitic, eight hyperpætic, and twelve myocardial. There was no heart disease other than the arrhythmia in fifty-nine, though four of these had a goiter.

The rate was between 160 and 200 in nearly half; it was between 140 and 240 in 90 per cent, but occasionally outside this wide range. There was no great difference between the various etiological groups. Nodal attacks tended to be a little slower and ventricular attacks were rather more often above 190, but even above this rate ventricular attacks formed a small minority.

Paroxysms are generally of short duration, lasting for hours rather than for days. In sixty-one the customary duration was less than two hours, and in another twenty-eight twelve hours or less. There were four where it was about twenty-four hours, and only seven where it was longer than this. But eighteen others, making twenty-nine in all, sometimes had attacks lasting more than one day, viz., over twenty-four hours, ten cases; two or three days, eight cases; up to seven days, four cases; up to ten days, five cases; and two to four weeks, two cases. One-third, therefore, of our patients had some attacks lasting more than a day, 10 per cent rarely, 10 per cent often, and 10 per cent habitually. Long attacks included an undue proportion of the ventricular paroxysms and were more common in those with myocardial disease.

Paroxysmal tachycardia is a symptom rather than a disease. In a minority of patients it accompanies serious heart disease, when, of course, the prognosis is grave. Such cases are nearly always under observation for their heart disease before the onset of paroxysms. Ventricular paroxysms form a fairly large proportion of this group and are rare otherwise. In most patients paroxysmal tachycardia is not in itself of any grave significance. It is due to reflex causes more often than to any primary change in the heart muscle. This applies not only to the majority whose hearts are otherwise normal but also to most of those with rheumatic heart disease and to some of those with other myocardial disease.

There is no close association between paroxysmal tachycardia and paroxysmal auricular fibrillation. In some of the rheumatic cases and less often in others, paroxysms of fibrillation may alternate with or replace paroxysms of tachycardia. In the rheumatic cases established fibrillation becomes a possibility in the near future.

The prognosis of paroxysmal tachycardia as regards life is, therefore, excellent, unless it is of the rare ventricular type, unless appearing relatively late in life it is the first indication of disease of the coronary arteries, or unless before the paroxysms have started there is already serious heart disease. Three of these patients have lived fifty years after the onset of their paroxysms, another eighteen for more than twenty years, and another twenty-six, making 47 per cent for more than ten years, and most of these are still in good health. Paroxysmal tachycardia does not produce heart disease, even when it continues throughout life, though one possible exception to this statement has been quoted. In general the prognosis depends on the condition of the heart muscle and should be decided without reference to the paroxysms. There is no constant tendency for the paroxysms to get worse as life advances, and usually some form of treatment can be found which will reduce the frequency and the discomfort produced by the attacks.

AUTHORS.

Mortensen, Vagn: On the Pathogenesis of Bundle Branch Block as Elucidated by the Elektrocardiographic Changes in Precordial Leads. Remarks on the Relation Between Bundle Branch Block and Other Preponderance Curves in Precordial Leads, and on the Relation of the Latter to Infarction Curves. Nordisk Medicin 1: 1971, 1939.

The electrocardiograms in standard and precordial leads in sixteen cases of bundle branch block are described. It is pointed out that there exists a great deal of conformity between the ventricular complexes in Lead IV_r in complete left bundle branch block (new terminology) and in Lead CF_2 in complete right bundle branch block and in curves belonging to Bayley's groups; this may suggest that curves belonging to Bayley's groups represent complete right bundle branch block.

Attention is called especially to the diminution or the absence of the R wave in Lead CF_2 in left bundle branch block. A similar configuration has been found in pronounced left ventricular preponderance. On account of these observations the hypothesis is advanced that the normal relation between the amplitudes of the R waves in CF_2 and IV_r depends on a certain normal relation between the conduction through the two ventricles, and that the diminution of the R wave which may be found in pronounced left ventricular preponderance and especially in left bundle branch block is caused by a lesser or greater relative delay of the conduction through the left ventricle, owing either to lesions in the conduction system or to hypertrophy of the left ventricle.

In standard leads the changes characteristic of pronounced left ventricular preponderance—that is, essentially, the curves described by Luten and Grove and by Rykert and Hepburn—were formerly explained in part by the hypertrophy of the left ventricle, partly by changes in the heart's position caused by the hypertrophy, and finally, owing to the resemblance between these curves and bundle branch block, by intraventricular conduction delay, which with the old terminology for bundle branch block must be localized to the right ventricle (Luten and Grove); still, Fahr and Mann and Weber have assumed that a possible delay of conduction had to be located on the left side. With the old terminology for bundle branch block, these causes, hypertrophy of the left ventricle and intraventricular conduction delay, could be considered from the same point of view only with difficulty.

The new terminology for bundle branch block is bringing quite new perspectives for the understanding of the preponderance curves. The plain transition between left preponderance curves and left bundle branch block (new terminology) makes it most likely that pronounced left preponderance curves are caused by a lesser degree of delay of the conduction through the left ventricle than is the case in left bundle branch block. Such a lesser degree of delay of the conduction is in most cases explainable by the hypertrophy of the left ventricle. Thus the new terminology for bundle branch block brings the different theories about the cause of preponderance curves into a more likely connection with each other than is allowed by the old terminology. Surely hypertrophy of the left ventricle is a very essential factor in most cases of pronounced left preponderance curves and the delay of conduction is then secondary hereto. But setting the relative delay of conduction as the immediate cause of the preponderance curves, it will be possible to explain also the cases of preponderance curves which are not accompanied by hypertrophy of the left ventricle. For a delay of conduction need not necessarily be due to ventricular hypertrophy but may be due to lesions in the conduction system.

Attention has been drawn to the fundamental difference between absence of the R wave in CF_2 in left bundle branch block or pronounced left ventricular

have made no new observation in this regard, but they have done well to emphasize it. The beneficial effects of sympathectomy on blood pressure cannot, apparently, be judged by the value of the blood pressure shortly after operation and many of those who have reported their results of sympathectomy for hypertension do not even include these values for blood pressure in their presentations. The proof of value of an operative procedure in influencing blood pressure depends on whether or not the blood pressure is persistently reduced when patients return to normal activity after operation. Study of the author's data indicates that of the twenty-seven patients studied the blood pressure was significantly lower several years after operation than before in only seven instances. Each of these late blood pressure determinations was made when the patient returned to the hospital when congestive failure or other manifestations occurred, a time at which one might reasonably expect blood pressure to be lower as a result of rest and congestive failure. In evaluating the effects of any operations on arterial blood pressure it seems inadvisable to compare pressures during activity when patients were in good enough physical condition to warrant operation with those obtained later when they had congestive failure or other manifestations. The authors have performed a service by emphasizing the need for careful evaluation of results, but they have apparently committed the same error which they attribute to those who have reported results of operations on the sympathetic nervous system of patients with essential hypertension.

ALLEN.

Maher, C. C., and Wosika, P. H.: Urologic Hypertension. A Study of 101 Cases. Proc. Inst. Med., Chicago 12: 388, 1939.

In 600 hypertensive patients, the authors found that 101 exhibited a wide variety of urologic lesions. One quarter of these (26 cases) suffered from "parenchymal renal disease such as glomerulonephritis," and the rest showed a variety of infectious and obstructive lesions. Hydronephrosis was common due to a variety of lesions. In the list of lesions were such conditions as pyelonephritis, renal stone, and even urethral stricture. The point made is that each case of essential hypertension deserves a thorough urological examination.

STEELE.

Opsahl, Roald: On the Pathogenesis of Arterial Hypertension With Especial Regard to the Role of the Kidney and Adrenals in the Mechanism of White High Blood Pressure. Acta Med. Scandinav. Suppl. xcii. 1938, 262 pp.

Part I. Physiological Regulation of Arterial Pressure

In the first few pages Opsahl records recent evidence for his premise that essential hypertension is due to a constriction of the peripheral arterioles not dependent upon nervous regulation but upon "intrinsic spasm" of the musculature. He defines the disease about which he wishes to talk ("Blutdruckkrankheit") by indirection and says, "The concept can be delimited by excluding conditions known to be or provisionally accepted as causes of hypertension. . . ." In this way he avoids the nosologic error of considering what is left as a single entity.

Beginning with Allbutt's break, in 1895, from the view of Traube that all hypertension was conditioned by renal disease, he briefly leads up to Volhard's concept of "red" and "white" hypertension, and then states his own view in the form of a working hypothesis as follows: Persistent arterial hypertension

The main conclusions are:

1. Three pathogenetic mechanisms underlying chronic hypertension can be distinguished: (1) A purely constitutional one, (2) a pure renal one and (3) a combined one (constitutional hypertension "provoked" or brought out by a renal factor). The constitutional hypertension corresponds to Volhard's "red," the other two to "white" hypertension.

2. A renal hypertension is a compensatory phenomenon for relative filtration-insufficiency (not failure of the excretory function). When hypertension can no longer compensate for the *filtration*-insufficiency, then *renal* insufficiency may be said to exist.

3. The increase in size of adrenal glands agrees with the modern conception of the role of these organs in regulating arterial pressure and can be regarded as necessary for meeting the chronic emergency of renal filtration-insufficiency by compensating for it with a persistent elevation of arterial pressure.

STEELE.

Horn, Henry, Dack, Simon, and Friedberg, Charles K.: Cardiac Sequelae of Embolism of the Pulmonary Artery. Arch. Int. Med. 64: 296, 1939.

A group of forty-two cases of embolism of the pulmonary artery has been studied, in eight of which recent structural changes in the myocardium ordinarily resulting from acute myocardial ischemia were revealed.

The factors necessary for the production of such myocardial changes are discussed. These are shock, asphyxia, and exaggerated vagal reflexes resulting from obstruction of the pulmonary arteries. These factors, alone or in association, lead to insufficiency of the coronary circulation. Morphologic evidence of coronary insufficiency in cases of embolism of the pulmonary artery is more likely to occur if there are recurrent embolization, narrowing of the coronary arteries, cardiac hypertrophy, and adequate duration of life after embolism.

Anatomic changes in the myocardium in persons with embolism of the pulmonary artery may be considered the end result of the myocardial ischemia which accounts for the characteristic electrocardiographic changes.

The resemblance of electrocardiographic changes in cases of embolism of the pulmonary artery to those in cases of myocardial infarction of the posterior wall may be explained by the diminished flow through the right coronary artery resulting from increased tension in the right ventricle.

AUTHORS.

Gregg, Donald E., Thornton, John J., and Mautz, Frederick R.: The Magnitude, Adequacy and Source of the Collateral Blood Flow and Pressure in Chronically Occluded Coronary Arteries. Am. J. Physiol. 127: 161, 1939.

The results presented elucidate in part what happens dynamically in the vascular bed of a chronically occluded coronary artery in favorable dogs and have led to the belief that a large new collateral circulation develops. Our criteria for such a belief are the recorded experimental facts that (1) in twenty-two of twenty-three dogs the peripheral coronary pressure is greatly increased (as compared to normal controls) and at times to values even approaching aortic pressures; (2) the retrograde blood coming from the peripheral end of the occluded coronary ranges up to 105 c.c. per minute with most of the values around 30 to 40 c.c. per minute; (3) the retrograde blood is so similar to arterial blood that it cannot be differentiated on the basis of its carbon dioxide and oxygen content, and (4) such volume flows of arterial blood are sufficient for the met-

abolic needs of the potentially infarcted myocardium, for the myocardial region exhibits normal contractions except in areas of scarring.

No single pulse pattern or set of ordinate values exists in the peripheral ends of the major coronary rami chronically ligated. The most usual peripheral coronary pressure is similar in timing and contour (although greater in magnitude) to the normal curve obtained immediately after coronary ligation, others more nearly resemble an intraventricular pressure curve while less frequently the peripheral coronary pressure curve can scarcely be distinguished from the aortic curve simultaneously recorded.

From an analysis of these coronary pulse patterns the conclusion is drawn that most of the collateral flow occurs during diastole and that only in those coronary pressure curves which resemble the aortic in ordinate values and contour can the source of the retrograde blood be predicted.

By clamping the other coronaries either separately or together while measuring the retrograde flow in the third coronary chronically occluded, the functional extent of the newly established coronary anastomoses has been determined. It has been found that:

The descendens receives on an average 62 to 66 per cent of its collateral flow from the other coronaries (right 7 per cent and circumflex 55 per cent).

The circumflex receives 66 to 64 per cent from the other coronaries of which the right and descendens contribute 19 and 47 per cent.

The right receives 97 to 79 per cent of its flow from the left coronary artery, the descendens contributing 22 per cent and the circumflex 75 per cent.

This leaves a large residual flow in the left coronary and a small residual flow in the right still to be accounted for. The origin of this potential extra-coronary retrograde flow has not been determined.

AUTHORS.

O'Shaughnessy, Laurence, Slome, David and Watson, F.: Surgical Revascularization of the Heart. *Lancet* 2: 617, 1939.

Histologic and injection studies are presented, demonstrating that vascular connections will develop between the vessels of the myocardium and extracardiac vessels (a) when cardiopericardial adhesions are produced with aleuronat; (b) when a pedicled omental graft is introduced into the pericardial sac and adhesion between omentum and heart is stimulated with aleuronat; and (c) when omentum is grafted to the outer surface of the pericardium after the production of cardiopericardial adhesions.

Collateral communication will develop between the pulmonary and coronary circulations if a lobe of the lung is grafted to the myocardium.

AUTHORS.

Flothow, Paul G.: The Surgical Treatment of Essential Hypertension. *Am. J. Surg.* 44: 535, 1939.

The preoperative testing and surgical treatment of patients with essential hypertension are reviewed. The results of operations on twenty-two patients are presented.

The author believes that there is no other method of treatment of essential hypertension that offers anything comparable to the results following extensive sympathectomy in selected patients. Postoperative blood pressure cannot be the only criterion of results accomplished since many patients who exhibit no fall in blood pressure are markedly improved clinically and symptomatically.

NAIDE.

Spink, Wesley W., and Crago, F. Hughes: Evaluation of Sulfanilamide in the Treatment of Patients With Subacute Bacterial Endocarditis. Arch. Int. Med. 64: 228, 1939.

It appears from the foregoing observations that the administration of sulfanilamide to patients with subacute bacterial endocarditis will in some instances render the circulating blood free of organisms. Except for two of the patients, this bactericidal effect was only temporary and depended on the continued use of the drug. In two patients definite improvement followed the use of sulfanilamide. However, we believe that sulfanilamide and its related compounds will be of doubtful value in the treatment of patients with subacute bacterial endocarditis because of the very nature of the focus of infection. The proliferating mass of bacteria situated well beneath the surface of the vegetation is probably protected, at least in part, from the action of free sulfanilamide in the blood, as well as of specific antibodies. When the organisms approach the surface of the vegetation, they are carried off in the circulating blood, and under these circumstances may be killed. An analogous therapeutic situation is now recognized in the treatment of patients with bacteremia due to beta hemolytic streptococci. Lockwood stated that in a number of instances of infection of the blood stream an infected thrombus in a large vessel has prevented satisfactory elimination of the bacteremia.

Since the presence of sulfanilamide in the blood may have a bacteriostatic effect on some strains of *Str. viridans*, sulfanilamide probably should be administered to any patient with valvular lesions who may be subjected to oral surgical procedures. It is well known that after the extraction of teeth or after a tonsillectomy temporary bacteremia with *Str. viridans* may result.

AUTHORS.

Edwards, Edward A., Hamilton, James B., and Duntley, S. Quimby: Testosterone Propionate as a Therapeutic Agent in Patients With Organic Disease of the Peripheral Vessels. New Eng. J. Med. 220: 865, 1939.

Following the treatment of human male castrates with testosterone propionate there was an increase in arterialization and blood volume in the head, palms of the hands and soles of the feet. The vascular changes in the skin were observed with the recording spectrophotometer.

Seven male patients with organic vascular disease were then treated with crystalline testosterone propionate. Three of the men had thromboangiitis obliterans and four were arteriosclerotic. All had occlusion of major vessels. Administration of testosterone propionate produced favorable changes in all the patients. The spectrophotometer curves after treatment showed an early and decided arterialization of the cutaneous blood. Other beneficial effects were relief of night pain and improvement in intermittent claudication. These findings are presented as a preliminary report.

NAIDE.

Book Reviews

CLINICAL RADIOLOGY OF THE HEART AND GREAT VESSELS: By C. H. Laubry, P. Cottenot, D. Rositier, and R. Heim, Paris, 1939, Masson et Cie.

Those who during the last year have followed the abstract section of THE AMERICAN HEART JOURNAL will have been impressed with the importance of the studies on radiology of the heart which have come from Laubry's clinic. This work has now found a fitting climax in the two volumes which have just been issued. The authors' special contributions are here included in a comprehensive atlas, comprising practically all known information on the subject. The work does not follow the standard classification of heart disease, but is logically developed along radiologic lines.

The parts which the various chambers of the heart play in the formation of the cardiac shadow are clearly illustrated by the post-mortem injections with opaque media. The various types of normal hearts are considered, including kymographic studies. Consideration is given to the variations occurring at various ages, during pregnancy, and from extrinsic factors, such as pleural effusions, pulmonary fibrosis, thoracic deformities, and diaphragmatic hernias. It is shown how normal hearts may simulate mitral lesions.

A wealth of pictures illustrates rheumatic heart disease; how mitral lesions are consistent with normal heart shadows; the evolution of the lesions through the years; and how cardiac enlargement affects the mitral characteristics. Throughout, modern concepts of heart disease are applied to the interpretations. Changes in the pulmonary circulation and the hilus shadows are also shown. Special attention is given to enlargement of the left auricle and the part it plays in the formation of the right cardiac border. The shadow of the left auricle is shown superimposed on that of the rest of the heart. The displacement of the bronchi and the esophagus is shown by contrast media. Finally pictures are shown of multiple valvular involvements, pancarditis, and aortic regurgitation.

In the second volume the first sections are devoted to congenital heart disease. Rogers' disease, alone and in conjunction with other defects, pulmonary stenosis, coarctation of the aorta (not quite so plain as the rest), persistent ductus arteriosus, patent foramen ovale, transposition, and idiopathic hypertrophy—a full catalogue.

Next, the authors turn to aortitis and the degenerative changes, arteriosclerosis and the resulting deformities, of which an amazing collection is shown, senile changes, and aneurysms in all forms and locations. The text here contains a valuable discussion of the diagnostic signs, including a kymographic discussion. Then come myocardial disease, coronary infarction, and cardiac aneurysm. Dilation of the pulmonary arteries is beautifully shown, also the effect of hypertension of long standing. Pericardial diseases are considered: effusions, adhesions, calcifications, and even a case of diverticulum. Cardiac insufficiency is illustrated including pulmonary edema during and following an attack. A few pictures demonstrate the technique of locating foreign bodies in the heart. The work closes with a collection of diagnostic problems.

Throughout, the very highest standards prevail; the photographs are as perfect as is technically possible. They show even fine shades of contrast and are beautifully reproduced. The text is condensed, yet adequate. Only one small

criticism may be leveled against the work: a considerable number of reference figures in the text have been misprinted. The volumes constitute a landmark in cardiac diagnosis and should find wide distribution.

JULIUS JENSEN.

PERIPHERAL VASCULAR DISEASES, DIAGNOSIS AND TREATMENT: By William S. Collens, M.D., Chief of the Clinic for Peripheral Vascular Diseases, Israel Zion Hospital, Brooklyn, N. Y., and Nathan D. Wilensky, M.D., Assistant in the above clinic. 243 pages, 1939, \$4.50, Springfield and Baltimore, Charles C. Thomas.

The aims of this book are presented in the preface. "This book has been planned to offer the physician a ready reference and a compendium which will aid him in the early recognition of peripheral vascular diseases and to offer him specific instruction in the management of the individual case." Since there is little or no consideration of diseases of the veins or lymph vessels, a more appropriate title would be "Peripheral Arterial Diseases." However, such a title would not be quite accurate, for aneurysm, glomus tumors, periarteritis nodosa, and arteriovenous fistula, for example, are considered minimally or not at all. The bibliography is incomplete; many important contributions are not mentioned. The term "peripheral vascular sclerosis," used to designate "peripheral arteriosclerosis," is an example of loose exposition. While the authors have attributed inflammation of peripheral arteries to syphilis, rheumatism, tuberculosis, pneumonia, and typhoid fever, they present no evidence that this actually occurs. The chapters on "Methods of Examination" and on "Symptoms and Signs of Interference With Arterial Flow" are fairly complete. The chapters in which methods of treatment are evaluated have much merit. The reviewer can offer objections to relatively minor points. Three examples follow: The few words on sympathicotonia do not clarify this elusive or nonexistent syndrome. The application of the term "nocturnal claudication" to "nocturnal cramps" serves only to confuse. Nocturnal leg cramps by no means affect only individuals with diabetes, as the authors imply. The statement is made that it is important to differentiate "peripheral vascular sclerosis" from thromboangiitis obliterans, but no reasons are given.

It is logical that the authors should devote a good deal of space to intermittent venous occlusion, a method of treatment which they originated, but it is unfortunate that comparatively little should be written of other methods of treatment which some authorities regard as more efficacious. The unfortunate intimation that the authors recently originated the test for determining the distance patients must walk to produce claudication overlooks publications of several years ago in which this test was described by others. The authors' question whether the improvement noted during treatment of thromboangiitis obliterans with repeated intravenous injections of hypertonic salt solution is not due to spontaneous regression of the disease might well be asked with respect to the use of intermittent venous occlusion.

The book is attractively printed.

EDGAR V. ALLEN.

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The income from membership and donations provides the sole support of the Association. Lack of adequate funds seriously hampers more widespread educational and research work imperative at this time. Great progress has been made, but much remains to be done.

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*Executive Committee.

The American Heart Journal

VOL. 18

NOVEMBER, 1939

No. 5

Original Communications

THE RATE OF THE CIRCULATION IN THE ARTERIES AND VEINS OF MAN

I. STUDIES OF NORMAL SUBJECTS AND OF THOSE WITH OCCLUSIVE ARTERIAL DISEASE AND HYPERTHYROIDISM*

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ROCHESTER, MINN.

KOCH,¹ in 1922, was the first investigator to determine the speed of circulation in man. He injected a solution of potassium ferrocyanide into the cubital vein of one arm and collected samples of blood from the cubital vein of the other arm at five-second intervals. He found that the average time required for the blood to traverse such a circuit was twenty-two seconds, with a range of twelve to twenty-seven seconds in different individuals. Since that time, numerous other methods have been introduced for estimating the velocity of the blood flow. An active radium deposit has been injected into a vein at the elbow and its arrival at the opposite brachial artery detected by means of a counting chamber.² Calcium chloride,³⁻⁶ calcium bromide,⁷ calcium gluconate,^{8, 9} endoiodine,¹⁰ and magnesium sulfate^{11, 12} have been injected intravenously, and the interval elapsing between the injection of the solution and the occurrence of a warm sensation in the throat has been considered the circulation time between the arm and the tongue. Dehydrocholic acid (decholin¹³⁻²²), which causes a bitter taste in the mouth, and saccharin,²³⁻³¹ which causes a sweet taste in the mouth, have also been utilized for determining the speed of blood flow between these same two points. Various dyes have been injected intravenously and the speed of blood flow determined by analyzing samples of blood collected from the carotid, femoral, and radial arteries.³²⁻³⁶ Histamine has been utilized to determine the circulation time between a vein of the arm or foot and the capillaries of the face.³⁷⁻³⁹ Sodium cyanide, which causes a sudden

*Abridgment of thesis submitted by Dr. Kvale to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine.

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Received for publication June 20, 1939.

deep inspiration after its intravenous injection, has been used to estimate the circulation time⁴⁰⁻⁴⁷ from the arm to the carotid sinus. Ether and paraldehyde have been employed to measure the pulmonary circulation time.⁴⁸⁻⁵¹

These methods have, for the most part, dealt almost entirely with the velocity of the blood flow in the peripheral venous and pulmonary systems. Exceptions are to be found in the works of Hamilton, Moore, Kinsman, and Spurling,³²⁻³⁵ of Blumgart and Yens,⁵² of Klein and Heinemann,³³ and of Robb and Weiss,⁴⁵ whose investigations included speed of flow of blood in peripheral arteries, as well. No attempts were made to estimate the speed of flow of blood in the arteries alone, although Blumgart and Weiss did assume that 3.3 seconds are required for the blood to flow from the left ventricle to the brachial artery.

In 1929, Kahler,⁵ by timing the occurrence of the warm sensation in the tongue, perineum, hands, and feet after the intravenous injection of calcium chloride, measured for the first time the velocity of the flow of blood in a combined venous-arterial circuit. Leschke⁶ and Katz⁷ confirmed Kahler's work. In 1936, Spier, Wright, and Saylor⁵³ utilized the same principle by means of a solution containing magnesium sulfate, calcium gluconate, and sodium chloride.

Thus, it is apparent that methods for determining the speed of flow of blood in the arteries of man are lacking. It has, therefore, been the purpose of this investigation to determine, if possible, the speed of the flow of blood in both the arteries and the veins of a group of individuals considered to have normal circulation, and in groups suffering from occlusive arterial disease and hyperthyroidism.

THE SOLUTION AND METHOD OF STUDY

Constituents of the Solution and Its Mode of Action.—The solution we have used is that described by Spier, Wright, and Saylor.^{53*} It contains 42 gm. of magnesium sulfate, 16 gm. of calcium gluconate, 0.9 gm. of sodium chloride, and 1.0 mg. of copper sulfate in each 100 c.c. of distilled water. The reasons for using a solution containing these ingredients have been discussed by Spier, Wright, and Saylor. The magnesium sulfate is used because of the subjective sensation of warmth that it produces, and the calcium gluconate and sodium chloride are added to minimize any possible toxic effects of the magnesium salt. Copper sulfate is added to the solution solely as a preservative. When this solution is injected intravenously, it produces a sensation of warmth or heat throughout the body, but particularly, and usually very distinctly and unmistakably, in the throat, perineum, hands, and feet. The exact mechanism involved in the production of this burning sensation is not known.

Description of the Method.—Before the test is performed, the subject is carefully instructed what to expect. He is told that something is to be injected into his vein, that it will produce a sensation of warmth throughout his body in less than a minute, but that separate from this general feeling of body warmth he will feel distinctly a flash of heat in his throat, perineum (crotch), hands, and feet. In some instances the subject feels only the flash of heat in the sites mentioned.

*The solution was made available through the courtesy of Merck and Co., Rahway, N. J.

He is requested not to become confused, but to pay close attention, for, although the sensation is not exactly pleasant, it is certainly not unpleasant. He is instructed to report immediately the site of the sensation by saying sharply, "tongue," "crotch," "hands," or "feet." In a subject with a normal circulation the sensation that occurs in the hands usually appears simultaneously in both. This likewise holds true for the feet. The subject is told this, but it is also made clear that the sensation may occur in one hand before it occurs in the other, or in one foot before it occurs in the other. Under these circumstances he should say, for example, "right foot," or "left foot."

Two cubic centimeters of the solution described previously are drawn into a 3 c.c. syringe which has been fitted with a 20-gauge needle. With the patient at rest and the arm at the level of the heart, the needle is inserted into a vein overlying the antecubital fossa. After the tourniquet has been released, a pause of three to five seconds is made before the solution is injected. This is done to allow the circulation to return to its original state in case it has been disrupted by the tourniquet or by any mechanical manipulation of the needle. Then the solution is injected as rapidly as possible. When the injection is started, the demonstrator, or person performing the test, says the word, "go," and a helper starts the stop watch. The stop watch is then transferred to the demonstrator, and as the subject calls out the various sites where the sensation occurs, the time is taken and duly recorded by the helper. By this means, that is, with the aid of another person, we have been able to get more accurate results than if the test were performed by one person alone.

Occasionally, especially if the patient is the least bit unstable, the first test will be unsatisfactory because of the rapidity with which reactions occur, and because, despite explicit and careful instructions, the exact description of the sensation cannot be fully explained. This result, fortunately, is infrequent, and a second test, done within five or ten minutes, may prove to be perfectly satisfactory. In the usual case, however, only one test is necessary.

Definition of Terms.—What has been determined in all these studies is the time elapsing between the beginning of the injection into a vein and the occurrence of the sensation of warmth in the throat, hands, perineum, and feet, respectively. We wish to emphasize that we do not know that the sensation of warmth in the hands, for example, indicates that the solution injected has just arrived at the hands, but for the purpose of simplification we have assumed that this reasoning is correct. Thus the expressions "arm to tongue," "arm to hand," "arm to perineum," and "arm to foot" indicate the time elapsing between injection of the solution into a vein at the elbow and the occurrence of the sensation in the tongue, hands, perineum, and feet, respectively. Whenever patients failed to perceive the sensation of warmth, the designation "blank" has been used. Such periods of time as those indicated include the time required for the solution injected to pass through the arm vein, the superior vena cava, the right side of the heart, the pulmonary circulation, the left side of the heart and, finally, the peripheral arteries.

In this study we have been interested primarily in the speed of blood flow in peripheral arteries, but the test does not give any direct indication of this, for there is no way of knowing when the injected solution leaves the left ventricle. However, this can be estimated with reasonable accuracy. It seems reasonable to assume that by the time the solu-

tion reaches the tongue, it will have traversed a distance down the aorta equal to that between the left ventricle and the tongue. The time required for the blood to flow this distance appears to be about one second, although we cannot say that this is an established fact, and neither can we find any direct proof of this. Hamilton, Moore, Kinsman, and Spurling³² have considered that one second is required for blood to travel from the jugular vein to the heart. Since the total cross-sectional area of the great veins emptying into the right side of the heart is about twice that of the root of the aorta, and since the velocity of flow is inversely proportional to the cross-sectional area, the time required for the blood to flow from the left ventricle to the tongue appears to be even less than one second.

Because an unknown factor would be added in calculation of the time required for blood to traverse peripheral arteries, we have not included the assumed and reasonably correct time of one second required for blood to flow from the left ventricle to the tongue in our calculations. If we had done so, the "arm-to-foot time," minus "arm-to-tongue time," plus one second, would give a figure indicating the time elapsing during the passage of the solution from the left ventricle to the feet. Since the time required for blood to traverse the distance from the left ventricle to the tongue is relatively constant, we have considered that it may be included in calculations for comparative purposes. Therefore, the "left-ventricle-to-perineum" time, or "ventricle-to-perineum" time, has been calculated by subtracting the "arm-to-tongue" time from the "arm-to-perineum" time. Similarly, "arm-to-hand" time, minus "arm-to-tongue" time, equals "ventricle-to-hand" time, and "arm-to-foot" time, minus "arm-to-tongue" time, equals "ventricle-to-foot" time. It is interesting to note that G. N. Stewart,⁵⁴ in 1894, used this same principle to demonstrate the rate of blood flow from the root of the aorta to the crural artery in the rabbit.

We emphasize again that the periods of time so designated are not actual, but subject to the qualifications noted in the foregoing. By this method we have made an attempt to evaluate the speed of flow of blood throughout the arterial system—from the left ventricle to the hands, perineum, and feet. We are fully aware that the figures so obtained are not absolutely accurate, and that the designation "ventricle-to-hand" time, for example, is not an entirely true one, but we do feel that for the first time an attempt has been made to demonstrate the velocity of the flow of blood in the arteries of man.

Value of the Method.—There are certain qualifications which are essential to a good method of injecting any substance intravenously for circulation-time studies. These are enumerated below, and it is our opinion that the method we have been using fulfills these requirements.

1. *The substance must be nontoxic in the amounts utilized.* Neuwirth and Wallace^{55, 56, 57} have shown that the narcosis obtained from mag-

nesium salts is dependent upon the dosage and absorption of magnesium and the concentration of magnesium in the serum. They concluded that symptoms of depression in the dog appear only when the serum magnesium content reaches 5 mg. per 100 c.c., and that this also holds true for man. They stated that 0.25 gm. of magnesium sulfate per kilogram of body weight is the minimal effective dose in man, and that such a dose will raise the serum magnesium to 5.6 mg. per 100 c.c.

Since the amount of magnesium contained in the solution we have been using is but 0.84 gm. per 2 c.c., a normal person weighing 70 kg. would be receiving but 0.012 gm. of magnesium per kilogram of body weight, a safe working margin, and far below the dose, even if repeated many times in one day, required to produce slight depression. The amount of calcium injected is small and, we believe, should occasion no concern.

2. *The substance should be eliminated from the system quickly and easily, so that repeated tests may be performed without jeopardizing the welfare of the patient.* Mendel and Benedict,^{58, 59} in their work on the paths of excretion of inorganic compounds, showed that there is only a small excretion of magnesium sulfate into the intestines following subcutaneous injection into animals, and that the kidneys are predominantly important in the elimination of the excess magnesium sulfate. Furthermore, this excretion takes place within forty-eight hours, chiefly during the first twenty-four hours. They showed also that the increased excretion of magnesium by the kidneys is accompanied by a marked rise in the urinary output of calcium. It seems established, therefore, that the principal components of the solution we have injected are excreted from the body probably within twenty-four hours, chiefly by way of the kidneys.

3. *The substance should have no effect upon the pathologic condition being studied.* In our studies, we have perceived nothing to indicate that the injected solution influenced the various diseases that some of the patients had.

4. *The procedure should in itself be simple, and when the end point is subjective it should be comprehended easily by the person on whom the test is done.* This is true for the test that we have used except under circumstances that will be mentioned later.

Fallacies of the Method.—Objection may be offered to any method, such as the one we have described, which depends for accuracy on the patient's cooperation and ability to signal the sensation. Moreover, the exact mechanism by which the sensation is produced is still undetermined. It is not known whether the sensory nerves are stimulated at the instant the blood bearing the solution reaches the hand, for example, or whether the stimulation occurs some time later. Certainly the solution must stimulate sensory nerve endings either in the walls of the vessels or in the perivascular tissues. Whatever the mechanism, some time must be required for stimulation of the sensory nerves and perception of the

sensation. Although we believe that this "reaction time" is short, the method may be criticized because we do not know exactly what the reaction time is. To support the accuracy of the method one would need to prove that the reaction time is negligible, which we cannot do. If the reaction time were known to be constant under the conditions of our study, comparative values for speed of circulation could be determined. Unfortunately, we do not know that the reaction time is constant.

Hewlett,⁶⁰ Hewlett and Van Zwaluwenburg,⁶¹ Freeman,⁶² and Prinzmetal and Wilson,⁶³ by the use of the plethysmograph, and Stewart,⁶⁴ Taylor,^{65, 66} and Pickering,⁶⁷ by means of the calorimeter, have made valuable observations upon the volume, not velocity, of peripheral blood flow. We feel that the disadvantages of the test used by us, namely, that it is subjective, and that the "reaction time" is unknown, are outweighed by the advantages, in that it allows us to calculate blood flow from the heart to the periphery in terms of speed.

Reactions.—In this entire study, 634 injections were made into 217 patients. The safety of the method was demonstrated by the fact that the reactions which occurred were very few and mild. In several instances in which a small amount of the solution infiltrated the perivascular tissues, considerable pain and a severe burning sensation, lasting for several hours, resulted, but there was no subsequent sloughing or necrosis. Venous thrombosis occurred in only two instances. We anticipated no trouble from extravascular injection, for earlier we had injected the solution into the extravascular tissues of rabbits' ears without producing reactions other than edema.

RESULTS OF STUDY

Normal Subjects.—One hundred sixty-five tests were performed on sixty normal subjects. A large number of these tests were carried out under "basal conditions," a term signifying that the subject had been at complete rest for at least half an hour, without food for at least eighteen hours, and was in a room the temperature of which was kept constant. These conditions did not obtain in the group of patients who were studied under "uncontrolled conditions."

1. *Under Controlled Conditions.*—The results shown in Table I give the frequency distribution and mean of seventy-three tests performed on thirteen subjects. The range of the "arm-to-tongue" time is not great, and the average, 13.7 seconds, although one second more rapid than that reported by Spier, Wright, and Saylor,⁵³ is nevertheless in close agreement with all other circulation time tests that depend upon a reaction in the tongue or throat.

The range of the times for "arm to hands," "arm to perineum," and "arm to feet" was considerably greater, especially so in the case of the "arm-to-feet" times. In general, those with the longer "arm-to-tongue"

times had longer "arm-to-feet" times. In a few instances, but seven to nine seconds elapsed from the time the sensation was perceived in the tongue until it was perceived in the feet. In other instances as much as forty-three seconds elapsed. That such a variability was possible in different individuals was at first something of a surprise, but as more and more tests were done it was soon noted that such variations were by no means rare. In fact, the literature on the time required for circulation over shorter distances than from arm to feet indicates that there is a wide variation in speed of blood flow in different individuals.

TABLE I
NORMAL SUBJECTS UNDER CONTROLLED CONDITIONS
(SEVENTY-THREE TESTS ON THIRTEEN SUBJECTS)

TIME IN SECONDS	NUMBER OF TESTS					
	ARM TO TONGUE	ARM TO PERINEUM	ARM TO R. HAND	ARM TO L. HAND	ARM TO R. FOOT	ARM TO L. FOOT
0-4	0	0	0	0	0	0
5-9	3	0	0	0	0	0
10-14	47	4	2	0	0	0
15-19	21	29	16	19	2	2
20-24	2	20	29	27	7	8
25-29	0	12	11	13	12	9
30-34	0	7	13	12	7	11
35-39	0	0	1	2	15	13
40-44	0	0	0	0	6	6
45-49	0	0	0	0	4	4
50-54	0	0	0	0	5	4
55-59	0	0	0	0	1	1
Blanks	0	1	1	0	14	15
Mean*	13.76±.20	21.22±.41	23.68±.43	23.60±.48	34.28±.85	34.0±.85
Stan. dev.*	2.65	5.14	5.41	6.08	9.73	9.57

*Time in seconds.

In the same individual, however, if the test can be done under conditions as nearly the same as possible from day to day, little variation is noted (Table II). In Case 1, the test was done at the same hour on the days as noted. The patient had had no breakfast and had rested for at least an hour. In Case 2, the test was done at different hours of the day and, although no heed was paid to whether or not the patient had eaten, he had been at complete rest for more than an hour. If the values for the skin temperature are charted on the ordinates, and the values for the "arm-to-hand" or "arm-to-foot" times are charted on the abscissae, there is shown to be a rough correlation between circulation time and skin temperature.

Studies of the time required for the blood to flow from the left ventricle to the designated sites are shown in Table III. In this series of cases, an average of 7.6 seconds was required for the blood to flow from the left ventricle to the perineum. The values fell largely between five and nine seconds. An average time of 9.8 seconds was required for the blood to flow from the left ventricle to the hand, and the variation was

even greater, that is, five to fourteen seconds. This greater variation was expected, for studies have shown that whereas a number of factors influence circulation in the hand, they probably influence circulation to the perineum very little. The "ventricle-to-foot" times cover a rather wide range, with the greatest number of values occurring between fifteen and twenty-four seconds, and with a mean of 20.6 and 20.3 seconds for the right and left foot, respectively. These calculations of "ventricle-to-hand," "ventricle-to-perineum," and "ventricle-to-foot" times are the first attempts to determine speed of arterial circulation in man, with the exception of the study of Blumgart and Weiss,⁶⁸ who estimated that 3.3 seconds are required for blood to flow from the left ventricle to the brachial artery.

TABLE III

NORMAL SUBJECTS UNDER CONTROLLED CONDITIONS
(SEVENTY-THREE TESTS ON THIRTEEN SUBJECTS)

TIME IN SECONDS	NUMBER OF TESTS				
	VENTRICLE TO PERINEUM	VENTRICLE TO R. HAND	VENTRICLE TO L. HAND	VENTRICLE TO R. FOOT	VENTRICLE TO L. FOOT
0-4	6	5	4	0	0
5-9	51	29	32	3	3
10-14	14	34	32	7	8
15-19	1	4	4	18	16
20-24	0	0	1	16	16
25-29	0	0	0	8	10
30-34	0	0	0	4	3
35-39	0	0	0	3	2
Blanks	1	1	0	14	15
Mean*	7.61	9.88	9.78	20.61	20.32

*Time in seconds.

2. *Under Uncontrolled Conditions.*—The subjects included hospital patients, usually at rest in bed, and workers and assistants about the laboratory. The tests were done after short periods of rest.

One hundred two tests were performed on fifty-one subjects (Table IV). The results agree favorably with those obtained when the patient was under controlled conditions, except that in this group the average "arm-to-foot" time was two seconds less. We have no explanation for this fact unless it be that most of these tests were done during the warm summer months, when the subject's surface temperature was influenced by the environmental temperature, which was greater than that of the constant-temperature room. As will be shown in a subsequent publication, environment exerts a great influence upon the circulation time to the extremities. The skin temperatures of patients who were at rest in a constant-temperature room at 25° C. were, as a rule, considerably lower than those of patients who were not at rest in a constant-temperature room. In the former group, the circulation times were consequently increased. Further analysis reveals that in the "controlled group" no sensations were perceived in the right and left foot in fourteen and fifteen instances in seventy-three tests, while in the "uncontrolled

group" the respective figures were twelve and thirteen, respectively, in one hundred two tests. The proportionate increase in "blanks"* in the "controlled group," as contrasted to the number that occurred in the "uncontrolled group," may have been due to the lower environmental temperatures at which the studies in the former were carried out. If the mean figures for the "arm-to-foot" times in the "controlled" and "uncontrolled" series of studies are dealt with statistically, no significant difference is found, for 34.28 minus 32.17, or 2.11 seconds, is less than three times the square root of the sum of the squares of the two probable errors, or 1.09.

TABLE IV
NORMAL SUBJECTS UNDER UNCONTROLLED CONDITIONS
(ONE HUNDRED TWO TESTS ON FIFTY-ONE SUBJECTS)

TIME IN SECONDS	NUMBER OF TESTS					
	ARM TO TONGUE	ARM TO PERINEUM	ARM TO R. HAND	ARM TO L. HAND	ARM TO R. FOOT	ARM TO L. FOOT
0-4	0	0	0	0	0	0
5-9	5	0	0	0	0	0
10-14	65	6	4	2	0	0
15-19	25	47	24	28	0	0
20-24	6	25	35	36	20	18
25-29	1	15	18	14	28	29
30-34	0	4	13	14	13	15
35-39	0	1	5	4	7	6
40-44	0	2	1	2	7	7
45-49	0	0	0	0	10	10
50-54	0	0	0	0	3	2
55-59	0	0	0	0	1	1
60-64	0	0	0	0	0	0
65-69	0	0	0	0	1	1
Blanks	0	2	2	2	12	13
Mean*	13.68±.24	20.99±.37	23.47±.40	23.47±.41	32.17±.69	32.02±.68
Stan. dev.*	3.52	5.52	6.00	6.09	9.72	9.46

TIME IN SECONDS	NUMBER OF TESTS				
	VENTRICLE TO PERINEUM	VENTRICLE TO R. HAND	VENTRICLE TO L. HAND	VENTRICLE TO R. FOOT	VENTRICLE TO L. FOOT
0-4	12	11	10	0	0
5-9	73	36	41	3	3
10-14	11	43	36	30	29
15-19	4	10	13	26	27
20-24	0	0	0	10	10
25-29	0	0	0	13	13
30-34	0	0	0	5	4
35-39	0	0	0	2	2
40-44	0	0	0	1	1
Blanks	2	2	2	12	13
Mean*	7.28	9.80	9.80	18.67	18.48

*Time in seconds.

The results of our study of these two groups of normal subjects lead us to believe, therefore, that when circulation-time tests are to be done on a group of individuals, it matters little whether these individuals are

*As stated in "Description of Terms," the term "blank" is used to designate failure of the patient to perceive the sensation of warmth.

under absolutely basal conditions or not, for the mean of the results under basal and nonbasal conditions will be insignificantly different. Obviously, in study of patients not under basal conditions, they should be given the opportunity to recover from any undue physical effort and excitement and kept as quiet as possible under the circumstances. And, naturally, if one is to compare results of repeated studies of one patient, the circumstances of the study should be as nearly identical as possible each time.

Thromboangiitis Obliterans.—In Table V are presented the results of twenty-three tests on fifteen patients suffering from thromboangiitis obliterans. These tests were carried out, as a rule, under basal conditions, although in a few instances the patient had recently had food. Analysis of these cases reveals that the "arm-to-tongue" time is very

TABLE V
THROMBOANGITIS OBLITERANS
(TWENTY-THREE TESTS ON FIFTEEN SUBJECTS)

TIME IN SECONDS	NUMBER OF TESTS					
	ARM TO TONGUE	ARM TO PERINEUM	ARM TO R. HAND	ARM TO L. HAND	ARM TO R. FOOT	ARM TO L. FOOT
0-4	0	0	0	0	0	0
5-9	0	0	0	0	0	0
10-14	10	1	0	0	0	0
15-19	13	9	5	6	0	0
20-24	0	6	8	5	2	2
25-29	0	4	8	5	3	2
30-34	0	2	1	4	2	2
35-39	0	1	1	3	2	0
40-44	0	0	0	0	0	0
45-49	0	0	0	0	1	0
50-54	0	0	0	0	2	2
55-59	0	0	0	0	1	2
60-64	0	0	0	0	0	1
65-69	0	0	0	0	0	0
70-74	0	0	0	0	0	0
Blanks	0	0	0	0	0	1
Mean*	14.48±.40	22.35±.87	23.74±.75	25.30±1.00	36.08±2.23	40.58±2.98
Stan. dev.*	2.86	6.22	5.30	7.13	11.92	15.33

TIME IN SECONDS	NUMBER OF TESTS				
	VENTRICLE TO PERINEUM	VENTRICLE TO R. HAND	VENTRICLE TO L. HAND	VENTRICLE TO R. FOOT	VENTRICLE TO L. FOOT
0-4	5	1	2	0	0
5-9	14	12	7	0	0
10-14	2	9	9	0	0
15-19	2	1	3	3	2
20-24	0	0	2	4	4
25-29	0	0	0	2	0
30-34	0	0	0	0	1
35-39	0	0	0	2	2
40-44	0	0	0	2	2
45-49	0	0	0	0	1
50-54	0	0	0	0	0
Blanks	0	0	0	0	0
Mean*	7.30	9.13	10.83	22.77	25.00

*Time in seconds.

slightly longer than that of normal subjects (Tables I and IV). Whether this finding is significant in a small group of cases is difficult to say. Spier, Wright, and Saylor⁵³ obtained similar results.

The average "arm-to-foot" time is increased slightly in thromboangiitis obliterans (Tables I, IV and V), and the range is greater. The number of "blanks" occurring in the feet in thromboangiitis obliterans comprises 45 to 50 per cent of the total number of tests, as compared with 19.2 per cent in the normal subjects. Since the perception of the sensation in the feet depends in large part on the warmth of the skin, and since the extremities in thromboangiitis obliterans are, on the whole, relatively cold, the explanation of this occurrence becomes immediately evident.

The average "arm-to-foot" time in thromboangiitis obliterans, 36.1 and 40.6 seconds, respectively (Table V), is less important than the results in individual cases, for the extent of the disease varied widely in different cases. We have observed that clinical evidence of marked impairment of arterial circulation is not necessarily associated with a prolonged "arm-to-foot" circulation time. However, it may be stated as a generalization that usually the circulation time is more prolonged in cases of severe ischemia than in cases of milder ischemia.

Our conclusions regarding use of this solution for diagnosis of, and prognosis in, thromboangiitis obliterans are that it has no value. The circulation time depends upon too many factors, such as the vasomotor control of the extremities. A normal person, for instance, may have no disease of his arteries, yet his extremities may be cold and the circulation time to his extremities may be prolonged, or no sensation at all may result.

The effect of fever induced artificially by intravenous injection of typhoid vaccine on the speed of blood flow is shown in Table VI. As

TABLE VI

EFFECT OF FEVER INDUCED BY INTRAVENOUSLY INJECTED TYPHOID VACCINE ON CIRCULATION TIME IN THROMBOANGIITIS OBLITERANS

CASE		ARM TO TONGUE	ARM TO PERI- NEUM	ARM TO R. HAND	ARM TO L. HAND	ARM TO R. FOOT	ARM TO L. FOOT
		TIME IN SECONDS					
1	Before fever	11	16	21	21	Blank	Blank
	During fever	11	15	18	18	Blank	26
2	Before fever	16	22	25	26	Blank	Blank
	During fever	14	20	21	17	26	35
3	Before fever	18	21	28	28	Blank	Blank
	During fever	16	23	27	27	38	46
4	Before fever	19	33	24	37	57	57
	During fever	17	32	29	28	42	42
5	Before fever	15	23	29	36	46	Blank
	During fever	12	19	17	17	25	32
6	Before fever	12	19	21	16	26	28
	During fever	11	15	13	14	18	18
7	Before fever	16	26	29	30	37	70
	During fever	16	27	30	30	39	40

expected, the results were not uniform, for the degree of vasodilatation induced by fever is not uniform in all extremities in thromboangiitis obliterans. Usually, however, fever increased the speed of circulation.

Arteriosclerosis Obliterans.—What has already been written in regard to speed of circulation in thromboangiitis obliterans applies in cases of arteriosclerosis obliterans, as well. The results of the studies are shown in Table VII. The average figures for "arm-to-tongue," "arm-to-hand," "arm-to-perineum," and "arm-to-foot" times are all prolonged when compared with the figures obtained in a study of normal subjects (Table IV). Perhaps this indicates a general slowing of circulation in individuals of advanced age with arteriosclerosis. The percentage of "blanks" in the feet was 52 and 41 per cent in the right and left foot, respectively.

TABLE VII
ARTERIOSCLEROSIS OBLITERANS
(TWENTY-SEVEN TESTS ON THIRTEEN SUBJECTS)

TIME IN SECONDS	NUMBER OF TESTS					
	ARM TO TONGUE	ARM TO PERINEUM	ARM TO R. HAND	ARM TO L. HAND	ARM TO R. FOOT	ARM TO L. FOOT
0-4	0	0	0	0	0	0
5-9	0	0	0	0	0	0
10-14	6	0	0	0	0	0
15-19	12	4	4	3	0	0
20-24	4	9	5	6	0	1
25-29	3	1	6	5	3	3
30-34	1	3	4	5	3	2
35-39	1	2	1	2	1	1
40-44	0	3	3	2	3	4
45-49	0	1	1	0	0	1
50-54	0	2	1	2	1	0
55-59	0	0	0	0	0	0
60-64	0	0	0	0	2	1
65-69	0	0	0	0	0	1
70-74	0	0	0	0	0	2
Blanks	0	2	2	2	14	11
Mean*	18.48±77	29.8±1.56	29.16±1.31	29.80±1.31	40.15±2.29	44.06±2.86
Stan. dev.*	5.93	11.53	9.68	9.68	12.25	16.97

TIME IN SECONDS	NUMBER OF TESTS				
	VENTRICLE TO PERINEUM	VENTRICLE TO R. HAND	VENTRICLE TO L. HAND	VENTRICLE TO R. FOOT	VENTRICLE TO L. FOOT
0-4	5	3	2	0	0
5-9	8	8	7	0	1
10-14	6	7	8	1	2
15-19	3	6	7	5	3
20-24	1	1	1	2	1
25-29	2	0	0	3	4
30-34	0	0	0	1	2
35-39	0	0	0	1	1
40-44	0	0	0	0	0
45-49	0	0	0	0	1
50-54	0	0	0	0	0
55-59	0	0	0	0	1
Blanks	2	2	2	14	11
Mean*	10.68	10.96	11.28	22.38	26.06

*Time in seconds.

It is to be expected that in these cases the circulation times will be prolonged, and that the percentage of "blanks" in the feet will be relatively large. However, in one case of rather marked sclerosis of the peripheral vessels in which both dorsalis pedis and posterior tibial arteries were occluded, the circulation time to the feet on two tests was on the fast side of normal. And in another case, in which occlusion of the popliteal artery had occurred six weeks previous to study, with obvious evidence of vascular insufficiency, repeated tests showed a more rapid circulation in the more affected leg than in the other. These experiences lead us to question the value of the test in cases of arteriosclerosis obliterans.

Hyperthyroidism.—It is known that in cases of hyperthyroidism the velocity of the peripheral venous blood flow is increased. Tables VIII and IX indicate that the speed of arterial circulation is also increased.

TABLE VIII

EXOPHTHALMIC GOITER AND ADENOMATOUS GOITER WITH HYPERTHYROIDISM
(THIRTY-ONE TESTS ON FOURTEEN PATIENTS)

TIME IN SECONDS	NUMBER OF TESTS					
	ARM TO TONGUE	ARM TO PERINEUM	ARM TO R. HAND	ARM TO L. HAND	ARM TO R. FOOT	ARM TO L. FOOT
0-4	0	0	0	0	0	0
5-9	9	0	0	0	0	0
10-14	22	14	9	7	1	1
15-19	0	17	16	19	10	10
20-24	0	0	5	5	6	6
25-29	0	0	0	0	7	7
30-34	0	0	0	0	0	1
Blanks	0	0	1	0	7	6
Mean*	10.39±.29	14.93±.34	16.23±.39	16.64±.35	21.29±.54	21.76±.64
Stan. dev.*	2.42	2.79	3.14	2.87	3.95	4.73

*Time in seconds.

TABLE IX

EXOPHTHALMIC GOITER AND ADENOMATOUS GOITER WITH HYPERTHYROIDISM
(THIRTY-ONE TESTS ON FOURTEEN PATIENTS)

TIME IN SECONDS	NUMBER OF TESTS				
	VENTRICLE TO PERINEUM	VENTRICLE TO R. HAND	VENTRICLE TO L. HAND	VENTRIC TO R. FOOT	VENTRICLE TO L. FOOT
0-4	15	8	6	1	1
5-9	16	22	25	9	9
10-14	0	0	0	12	12
15-19	0	0	0	2	2
20-24	0	0	0	0	0
25-29	0	0	0	0	1
Blanks	0	1	0	7	6
Mean*	4.58	5.76	6.25	10.58	11.28

*Time in seconds.

In exophthalmic goiter and adenomatous goiter with hyperthyroidism the average "ventricle-to-perineum" time is 4.6 seconds, the average "ventricle-to-hand" time is about six seconds, and the average "ven-

tricle-to-foot" time is about eleven seconds. In normal subjects under uncontrolled conditions (Table IV), the average "ventricle-to-perineum" time is 7.3 seconds, the average "ventricle-to-hand" time is 9.8 seconds, and the average "ventricle-to-foot" time is about 18.5 seconds. Apparently, the speed of blood flow in arteries and veins is similar; the factors that influence the former also influence the latter.

It is of interest that an increased volume flow of blood in the arm was first noted by Hewlett and Van Zwaluwenburg,⁶¹ in 1909, in cases of exophthalmic goiter. They stated, "We suspect that this acceleration of the peripheral rate of blood flow is a fairly constant feature of exophthalmic goiter and roughly proportionate to the severity of the disease." That this statement can be applied equally well to velocity of blood flow is shown by our results. The figures indicate, also, less variability of results in hyperthyroidism than in normal subjects.

CONCLUSIONS

1. A solution of magnesium sulfate, calcium gluconate, and copper sulfate, in a physiologic solution of sodium chloride, may be used safely for determination of the speed of circulation of blood from an arm vein to the throat, hands, perineum, and feet. However, there is no evidence that the sensation of warmth produced in the throat, hands, perineum, and feet indicates the arrival of the injected solution at these areas, for there is a "reaction time." In this study we have been aware of the possibility that this reaction time may be variable, and thus influence results, and that, even if it is constant, the figures we have obtained are valid only for comparative purposes. However, it appears that much information relative to the speed of blood flow in man may be gained by this method of study.

2. The average values obtained in normal subjects under controlled conditions are as follows: "arm-to-tongue" time, 13.7 seconds; "arm-to-perineum" time, 21.2 seconds; "arm-to-hand" time, 23.6 seconds; and "arm-to-foot" time, 34 seconds. The values obtained in normal subjects under uncontrolled conditions do not differ materially from those stated above, except that the average "arm-to-foot" time is 32 seconds.

3. The range of the "arm-to-tongue" time with this solution is greater than other "arm-to-tongue" circulation times. The range of the "arm-to-hand" time is greater than the range of the "arm-to-perineum" time. The range of the "arm-to-foot" time is greatest of all. These wide ranges demonstrate that the speed of blood flow varies widely in the same individual under different conditions, but under similar and basal conditions the velocity of flow is remarkably constant.

4. In cases of thromboangiitis obliterans and arteriosclerosis obliterans, the speed of blood flow to the hands and feet is usually diminished, usually depending upon the degree of vascular obliteration. Inconsistent results, however, lead us to believe that this circulation-time test cannot be used to diagnose occlusive arterial disease.

5. In cases of hyperthyroidism the speed of flow of blood is increased in the arteries as well as in the veins.

6. The "ventricle-to-perineum" circulation time has been calculated by subtracting the "arm-to-tongue" time from the "arm-to-perineum" time. Similarly, "arm-to-hand" time, minus "arm-to-tongue" time, equals "ventricle-to-hand" time, and "arm-to-foot" time, minus "arm-to-tongue" time, equals "ventricle-to-foot" time. These "times" from the "ventricle" are of course assumed, but they furnish the first means of calculating the velocity of arterial blood flow in man. In normal subjects under uncontrolled conditions, the average "ventricle-to-perineum" time is 7.3 seconds, the average "ventricle-to-hand" time is 9.8 seconds, and the average "ventricle-to-foot" time is 18.5 seconds.

REFERENCES

1. Koch, E.: Velocity of Blood Stream, *Deutsch. Arch. f. klin. Med.* 140: 39, 1922.
2. Blumgart, H. L.: The Velocity of Blood Flow in Health and Disease, the Velocity of Blood Flow in Man and Its Relation to Other Measurements of the Circulation, *Medicine* 10: 1, 1931.
3. Berinskaay, A. N., and Meerzon, T. L.: Value of Determination of Velocity of Circulation in functional Diagnosis of Circulatory System, *Klinicheskaya. Meditsina.* 13: 70, 1935. Abstr. in *J. A. M. A.* 104: 1680, 1935.
4. Hirschsohn, J., and Maendl, H.: Notiz zur Kenntnis der Hämodynamik beim Pneumothorax, *Beitr. z. Klin. d. Tuberk.* 49: 64, 1922.
5. Kahler, H.: Über Veränderungen der Blutumlaufzeit (Ein Beitrag zum Problem der Blutgeschwindigkeit), *Wien. Arch. f. inn. Med.* 19: 1, 1929-1930.
6. Leschke, Erich: Kreislaufzeit und Blutgeschwindigkeit, *München. med. Wehnschr.* 2: 2117, 1931.
7. Katz, George: Zur Methodik der Bestimmung der Kreislaufzeit, *München. med. Wehnschr.* 79: 2048, 1932.
8. Goldberg, S. J.: The Use of Calcium Gluconate as a Circulation Time Test, *Am. J. M. Sc.* 192: 36, 1936.
9. Goldberg, S. J.: Circulation Time as a Diagnostic Aid in Hyperthyroidism, *Ann. Int. Med.* 11: 1818, 1938.
10. Alvarez, C.: El tiempo de circulación y su medida clínica. Empleo de la endoiodina, *Rev. méd. del Rosario.* 23: 595, 1933.
11. Neurath, Otto: Untersuchungen über die Bestimmung der Blutumlaufgeschwindigkeit mit Magnesiumsulfat, *Ztschr. f. klin. Med.* 132: 134, 1937.
12. Zwillinger, L.: Über die Magnesiumwirkung auf das Herz, *Klin. Wehnschr.* 14: 1429, 1935.
13. Gargill, S. L.: The Use of Sodium Dehydrocholate as a Clinical Test of the Velocity of Blood Flow, *New England J. Med.* 209: 1089, 1933.
14. Kopp, Israel: The Velocity of the Blood Flow in Therapeutic Hyperpyrexia, *AM. HEART J.* 11: 475, 1936.
15. Macy, J. W., Claiborne, T. S., and Hurxthal, L. M.: The Circulation Rate in Relation to Metabolism in Thyroid and Pituitary States (Decholin Method), *J. Clin. Investigation.* 15: 37, 1936.
16. Means, J. H., and Lerman, J.: Hormonic Symptomatology of the Thyroid; to What Extent Is It Explicable on the Basis of Altered Metabolic Rate, *Endocrinol.* 19: 181, 1935.
17. Miller, H. R.: Clinical Observations on Pulmonary Blood Flow in Silicosis and Other Fibrotic Conditions of the Lungs, *Am. J. M. Sc.* 191: 334, 1936.
18. Rosenblum, Harold: Rate of Blood Flow in Patients Receiving Dinitrophenol, *J. A. M. A.* 104: 1592, 1935.
19. Tarr, Leonard, Oppenheimer, B. S., and Sager, R. V.: The Circulation Time in Various Conditions Determined by the Use of Sodium Dehydrocholate. *AM. HEART J.* 8: 766, 1933.
20. Winternitz, M., Deutsch, J., and Brüll, Z.: Eine klinisch brauchbare Bestimmungsmethode der Blutumlaufzeit mittels Decholininjektion, *Med. Klin.* 27: 986, 1931.

21. Winternitz, M., Deutsch, J., and Brüll, Z.: Eine klinisch brauchbare Bestimmungsmethode der Blutumlaufzeit mittels Decholinjektion (Erwiderung). *Med. Klin.* 28: 831, 1932.
22. Wood, Paul: Right and Left Ventricular Failure: a Study of Circulation Time and Venous Blood Pressure, *Lancet* 2: 15, 1936.
23. Candel, Samuel, and Rabinowitz, M. A.: Blood Velocity Rate and Venous Pressure in the Prognosis of Heart Disease, *Ann. Int. Med.* 10: 1000, 1937.
24. Drennan, L. M., Jr.: The Clinical Significance of the Blood Circulation Time as Determined by the Saccharin Test, *M. Ann. District of Columbia* 5: 238, 1936.
25. Fishberg, A. M., Hitzig, W. M., and King, F. H.: Measurement of the Circulation Time with Saccharin, *Proc. Soc. Exper. Biol. and Med.* 50: 651, 1933.
26. Greenstein, N. M., and Clahr, Jacob: Circulation Time Studies in Pregnant Women, *Am. J. Obst. and Gynec.* 33: 414, 1937.
27. Hurst, Allan, and Brand, M. A.: A Study of Venous Pressure and Circulation Time in Pulmonary Tuberculosis, *J. Thoracic Surg.* 6: 638, 1937.
28. Leinoff, H. B.: Complications Following Use of Saccharin and Ether as a Circulation Time Test, *J. A. M. A.* 105: 1759, 1935.
29. Oppenheimer, B. S., and Hitzig, W. M.: The Use of Circulatory Measurements in Evaluating Pulmonary and Cardiac Factors in Chronic Lung Disorders, *AM. HEART J.* 12: 257, 1936.
30. Webb, George, Scheinfeld, William, and Colin, Hyman: The Importance in Surgery of the Blood Circulation Time, *Ann. Surg.* 103: 460, 1936.
31. Wohl, M. G., and Ettelson, L. N.: III. Studies in Obesity: Effect of Dinitrophenol on Blood Velocity, *J. Pharmacol. and Exper. Therap.* 55: 439, 1935.
32. Hamilton, W. F., Moore, J. W., Kinsman, J. M., and Spurling, R. G.: Simultaneous Determination of the Pulmonary and Systemic Circulation Times in Man and of a Figure Related to the Cardiac Output, *Am. J. Physiol.* 84: 338, 1928.
33. Klein, O., and Heinemann, J.: Zur Messung der Strömungsgeschwindigkeit des Blutes beim Menschen, *Zentralbl. f. inn. Med.* 50: 490, 1929.
34. Moore, J. W., and Kinsman, J. M.: Studies on the Circulation: the Dye Injection Method. The Effect of Digitalis Upon Patients With Normal Cardiovascular Systems, *J. Lab. and Clin. Med.* 22: 165, 1936.
35. Moore, J. W., Kinsman, J. M., Hamilton, W. F., and Spurling, R. G.: Studies on the Circulation. II. Cardiac Output Determinations: Comparison of the Injection Method With the Direct Fick Procedure, *Am. J. Physiol.* 89: 331, 1929.
36. Thompson, W. O., Alper, J. M., and Thompson, Phebe K.: The Effect of Posture Upon the Velocity of Blood Flow in Man, *J. Clin. Investigation* 5: 605, 1928.
37. Bain, C. W. C.: Observations on the Speed of the Circulation, *Quart. J. Med.* 3: 237, 1934.
38. Bartels, E. C., and Powelson, M. H.: The Rate of the Circulation of the Blood in Vascular Diseases as Determined by the Use of Histamine, *Proc. Staff Meet., Mayo Clin.* 4: 217, 1929.
39. Weiss, Soma, Robb, G. P., and Blumgart, H. L.: The Velocity of Blood Flow in Health and Disease as Measured by the Effect of Histamine on the Minute Vessels. *AM. HEART J.* 4: 664, 1929.
40. Cohen, M. E., and Thomson, K. J.: Studies on the Circulation in Pregnancy. I. The Velocity of Blood Flow and Related Aspects of the Circulation in Normal Pregnant Women, *J. Clin. Investigation* 15: 607, 1936.
41. Ellis, L. B.: Circulatory Adjustments to Moderate Exercise in Normal Individuals, With Particular Reference to the Interrelation Between the Velocity and Volume of the Blood Flow, *Am. J. Physiol.* 101: 494, 1932.
42. Kissin, Milton, and Bierman, William: Influence of Hyperpyrexia on Velocity of Blood Flow, *Proc. Soc. Exper. Biol. and Med.* 30: 527, 1933.
43. Kopp, Israel: The Arm-to-Carotid Circulation Time in Prolonged Therapeutic Fever, *AM. HEART J.* 11: 667, 1936.
44. McGuire, Johnson, and Goldman, Fred: Apparent Increased Velocity of Blood Flow in Cases of Congenital Heart Disease With Septal Defects Having Right-to-Left Shunt, *AM. HEART J.* 14: 230, 1937.
45. Robb, G. P., and Weiss, Soma: A Method for the Measurement of the Velocity of the Pulmonary and Peripheral Venous Blood Flow in Man, *AM. HEART J.* 8: 650, 1933.

46. Robb, G. P., and Weiss, Soma: The Velocity of Pulmonary and Peripheral Venous Blood Flow and Related Aspects of the Circulation in Cardiovascular Disease; Their Relation to Clinical Types of Circulatory Failure, *AM. HEART J.* 9: 742, 1934.
47. Smith, L. A., and Allen, E. V.: Personal communication to the authors.
48. Candel, Samuel: Determination of the Normal Circulation Time from the Antecubital Veins to the Pulmonary Capillaries by a New Technic, *Ann. Int. Med.* 12: 236, 1938.
49. Hitzig, W. M.: Measurement of Circulation Time From Antecubital Veins to Pulmonary Capillaries, *Proc. Soc. Exper. Biol. and Med.* 31: 935, 1934.
50. Hitzig, W. M.: The Use of Ether in Measuring the Circulation Time From the Antecubital Veins to the Pulmonary Capillaries, *AM. HEART J.* 10: 1080, 1935.
51. Miller, H. R.: The Velocity of Blood Flow in Part of the Pulmonary Circulation, *Proc. Soc. Exper. Biol. and Med.* 31: 942, 1934.
52. Blumgart, H. L., and Yens, O. C.: Studies on the Velocity of Blood Flow. I. Method Utilized, *J. Clin. Investigation* 4: 1, 1927.
53. Spier, L. C., Wright, I. S., and Saylor, Leslie: A New Method for Determining the Circulation Time Throughout the Vascular System, *AM. HEART J.* 12: 511, 1936.
54. Stewart, G. N.: Researches on the Circulation Time in Organs and on the Influences Which Affect It. I. Preliminary Paper, *J. Physiol.* 15: 1, 1894.
55. Neuwirth, Isaac, and Wallace, G. B.: Blood Serum Magnesium in Magnesium Anesthesia, *J. Pharmacol. and Exper. Therap.* 33: 266, 1928.
56. Neuwirth, Isaac, and Wallace, G. B.: On the Use of Magnesium as an Aid in Anesthesia, *J. Pharmacol. and Exper. Therap.* 35: 171, 1929.
57. Neuwirth, Isaac, and Wallace, G. B.: A Note on the Absorption Serum Concentration and Narcotic Effects of Magnesium, *J. Pharmacol. and Exper. Therap.* 45: 109, 1932.
58. Mendel, L. B., and Benedict, S. R.: The Paths of Excretion for Inorganic Compounds. IV. The Excretion of Magnesium, *Am. J. Physiol.* 25: 1, 1909.
59. Mendel, L. B., and Benedict, S. R.: The Paths of Excretion for Inorganic Compounds. V. The Excretion of Calcium, *Am. J. Physiol.* 25: 23, 1909.
60. Hewlett, A. W.: The Effect of Room Temperature Upon the Blood-Flow in the Arm, With a Few Observations on the Effect of Fever, *Heart* 2: 230, 1910-1911.
61. Hewlett, A. W., and Van Zwaluwenburg, J. G.: The Rate of Blood Flow in the Arm, *Heart* 1: 87, 1909-1910.
62. Freeman, N. E.: The Effect of Temperature on the Rate of Blood Flow in the Normal and in the Sympathectomized Hand, *Am. J. Physiol.* 113: 384, 1935.
63. Prinzmetal, Myron, and Wilson, Clifford: The Nature of the Peripheral Resistance in Arterial Hypertension With Special Reference to the Vasomotor System, *J. Clin. Investigation* 15: 63, 1936.
64. Stewart, G. N.: Studies on the Circulation in Man: IX. The Blood-Flow in the Hands (and Feet) in Cases in Which Obvious Anatomical Differences Exist, *Arch. Int. Med.* 12: 678, 1913.
65. Taylor, N. B.: The Blood-Flow in Man as Estimated by the Calorimetric Method of Stewart, *J. Lab. and Clin. Med.* 7: 439, 1922.
66. Taylor, N. B.: Observations Upon the Blood-Flow in Man. II. Estimation of the Blood-Flow Through the Hands in Clinical Cases, *J. Lab. and Clin. Med.* 8: 153, 1922.
67. Pickering, G. W.: The Peripheral Resistance in Persistent Arterial Hypertension, *Clin. Sc.* 2: 209, 1936.
68. Blumgart, H. L., and Weiss, Soma: Studies on the Velocity of Blood Flow. VII. The Pulmonary Circulation Time in Normal Resting Individuals, *J. Clin. Investigation* 4: 399, 1927.

THE RATE OF THE CIRCULATION IN THE ARTERIES AND VEINS OF MAN

II. STUDIES OF HYPERTENSION, OF ORTHOSTATIC HYPOTENSION, AND OF THE EFFECTS OF SYMPATHECTOMY*

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THE solution used and the manner of measuring the speed of circulation in both the arteries and veins of man have been described in a previous communication.¹ In brief, the procedure consists in determining the time elapsing between the intravenous injection of a solution containing magnesium, calcium, and sodium salts and the occurrence of a sensation of warmth in the tongue, perineum, hands, and feet. The value and faults of the method have been described previously. The speed of flow of blood in the arteries carrying blood to the feet was estimated by subtracting the "arm-to-tongue" time from the "arm-to-foot" time, and in the arteries carrying blood to the hands by subtracting "arm-to-tongue" time from the "arm-to-hand" time.

Although our results are not in exact agreement with those published by Spier, Wright, and Saylor,² who introduced the use of this solution for the determination of the circulation time, we and they have established normal values for the circulation time throughout the vascular system.¹ It is the purpose of this publication to report our studies of speed of blood flow in essential hypertension, and to demonstrate the effect of sympathectomy and orthostatic hypotension on the speed of flow in peripheral arteries.

RESULTS AND COMMENT

Essential Hypertension.—Pickering³ and Prinzmetal and Wilson⁴ have shown, by means of Stewart's calorimeter and the plethysmograph, respectively, that the volume flow of blood in the forearm of the patient with essential hypertension is approximately equal to that in the patient with normal blood pressure. They made no observations on the volume flow in the foot. Steele and Kirk⁵ have demonstrated that the temperature of the skin of patients suffering from arterial hypertension does not differ significantly from that of normal individuals. Williams⁶ has verified these observations. These observations support indirectly the accepted evidence that there is vasoconstriction in essential hyperten-

*Abridgment of thesis submitted by Dr. Kvale to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine.

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Received for publication June 20, 1939.

sion, for if this were not present the increased blood pressure would increase the flow of blood through the arterioles and thus increase the temperature of the skin.

The average "arm-to-tongue" time of 14.4 seconds for patients with essential hypertension in our observations (Table I) compares favorably

TABLE I
PATIENTS WITH ESSENTIAL HYPERTENSION
(FIFTY-EIGHT TESTS ON THIRTY-SEVEN SUBJECTS)

TIME IN SECONDS	NUMBER OF TESTS					
	ARM TO TONGUE	ARM TO PERINEUM	ARM TO R. HAND	ARM TO L. HAND	ARM TO R. FOOT	ARM TO L. FOOT
0-4	0	0	0	0	0	0
5-9	0	0	0	0	0	0
10-14	31	2	0	0	0	0
15-19	23	20	14	15	2	2
20-24	4	18	24	23	5	5
25-29	0	10	11	10	6	5
30-34	0	4	5	6	6	6
35-39	0	0	1	1	11	12
40-44	0	2	0	0	8	7
45-49	0	0	0	1	4	5
50-54	0	0	0	0	3	3
55-59	0	0	0	0	0	1
60-64	0	0	0	0	1	0
65-69	0	0	0	0	1	1
Blanks	0	2	3	2	11	11
Mean*	14.44±.26	22.04±.56	22.83±.45	23.36±.51	36.36±.96	36.79±1.06
Stan. dev.*	2.96	6.23	5.00	5.68	9.79	10.82

*Time in seconds.

with the time of 13.7 seconds in normal subjects. The circulation times to the perineum and hands likewise fall within the range of normal. The average "arm-to-foot" time, however (36.4 and 36.8 seconds, respectively, for the right and the left foot), is about four seconds more than the average normal under uncontrolled conditions (32.2 and 32.0 seconds, respectively), and about two seconds greater than the average normal under controlled conditions (34.3 seconds and 34.0 seconds, respectively).¹ The "ventricle-to-hand" and "ventricle-to-foot" times, since they were computed from the above, agree in a similar manner with those of the normal subjects (Table II). If the results of the fifty-eight tests on patients with hypertension, who were not under strictly basal conditions, are compared with the average normal circulation time under uncontrolled conditions, the difference is statistically significant. However, the average "arm-to-foot" time in essential hypertension is only about two seconds longer than the average "arm-to-foot" time in normal persons under controlled conditions. This difference is statistically insignificant. Whether or not the difference indicates diminished peripheral blood flow in essential hypertension, we do not know, but the figures suggest this possibility.

TABLE II

PATIENTS WITH ESSENTIAL HYPERTENSION
(FIFTY-EIGHT TESTS ON THIRTY-SEVEN SUBJECTS)

TIME IN SECONDS	NUMBER OF TESTS				
	VENTRICLE TO PERINEUM	VENTRICLE TO R. HAND	VENTRICLE TO L. HAND	VENTRICLE TO R. FOOT	VENTRICLE TO L. FOOT
0-4	12	3	3	0	0
5-9	33	35	33	3	3
10-14	9	15	16	8	9
15-19	1	2	3	8	6
20-24	0	0	0	11	11
25-29	1	0	1	9	9
30-34	0	0	0	5	6
35-39	0	0	0	1	1
40-44	0	0	0	0	1
45-49	0	0	0	2	1
Blanks	2	3	2	11	11
Mean*	7.53	8.43	9.01	21.31	21.97

*Time in seconds.

The Effect of Sympathectomy.—At the Mayo Clinic the usual operation performed for the relief of essential hypertension consists of a two-stage resection of the splanchnic nerves with partial removal of the celiac ganglia and removal of the first and second lumbar sympathetic ganglia.^{7, 8} This procedure removes sympathetic nerve control of the lower extremities. Patients on whom this operation had been performed afforded us the opportunity to determine the rapidity of the blood flow to the feet in a sympathectomized and unsympathectomized extremity simultaneously, since only one side is operated on at one time. It further enabled us to determine the rapidity of blood flow in bilaterally sympathectomized extremities.

So far as we know, the results of our study of the effect of sympathectomy on the rapidity of blood flow in man are the first to be recorded. Brown⁹ has shown, however, that vasodilatation results from sympathectomy. Herrick, Essex, and Baldes¹⁰ have demonstrated that the volume flow of blood in the femoral artery of the dog, as measured by the thermostromuhr method, is about twice as great on the sympathectomized side as on the unsympathectomized side. Freeman¹¹ has shown, by means of the plethysmograph, that ten days after cervico-dorsal sympathectomy there is a rather marked increase in the volume flow of blood in the hand, and that this decreases as the time after operation increases. He likewise found an increased flow of blood when he blocked the sympathetic chain on one side with procaine. His final conclusions were that the increase in flow of blood to the sympathectomized hand is the result not only of the release of vasoconstrictor impulses, but also of a change in local tissue metabolism. Prinzmetal and Wilson⁴ likewise observed an increased blood flow in the forearm on the sympathectomized side.

The results of twenty-five tests done on thirteen patients with essential hypertension, seven to eighteen days after the first-stage sympathectomy, are recorded in Tables III and IV. The mean "arm-to-sympathectomized foot" time was nine seconds less than the mean "arm-to-unsympathectomized foot" time, and the mean "ventricle-to-sympathectomized foot" time is also nine seconds less than the mean "ventricle-to-unsympathectomized foot" time. Unquestionably, sympathect-

TABLE III
ESSENTIAL HYPERTENSION AFTER FIRST-STAGE SYMPATHECTOMY
(TWENTY-FIVE TESTS ON THIRTEEN SUBJECTS)

TIME IN SECONDS	NUMBER OF TESTS					
	ARM TO TONGUE	ARM TO PERINEUM	ARM TO R. HAND	ARM TO L. HAND	ARM TO SYMPATHECTOMIZED FOOT	ARM TO UNSYMPATHECTOMIZED FOOT
0-4	0	0	0	0	0	0
5-9	0	0	0	0	0	0
10-14	15	0	0	0	0	0
15-19	10	3	5	5	0	0
20-24	0	10	8	6	5	2
25-29	0	6	7	6	8	2
30-34	0	1	2	5	7	3
35-39	0	2	0	0	2	3
40-44	0	0	1	0	3	4
45-49	0	0	1	0	0	3
50-54	0	0	1	0	0	1
55-59	0	0	0	0	0	1
60-64	0	0	0	0	0	1
Blanks	0	0	0	3	0	5
Mean*	13.92±.25	23.88±.77	26.08±1.24	23.95±.65	30.12±.79	39.2±1.60
Stan. dev.*	1.82	5.74	9.18	4.51	5.84	10.63

*Time in seconds.

TABLE IV
ESSENTIAL HYPERTENSION AFTER FIRST-STAGE SYMPATHECTOMY
(TWENTY-FIVE TESTS ON THIRTEEN SUBJECTS)

TIME IN SECONDS	NUMBER OF TESTS				
	VENTRICLE TO PERINEUM	VENTRICLE TO R. HAND	VENTRICLE TO L. HAND	VENTRICLE TO SYMPATHECTOMIZED FOOT	VENTRICLE TO UNSYMPATHECTOMIZED FOOT
0-4	1	2	1	0	0
5-9	16	10	8	0	0
10-14	5	9	11	10	4
15-19	1	1	2	10	2
20-24	1	0	0	2	3
25-29	1	1	0	2	5
30-34	0	1	0	1	4
35-39	0	1	0	0	0
40-44	0	0	0	0	1
45-49	0	0	0	0	1
Blanks	0	0	3	0	5
Mean*	9.96	12.16	10.22	16.2	25.5

*Time in seconds.

tomy increases the speed with which blood flows through arteries. If one calculates the time for blood to flow from the iliac artery to the feet by subtracting "arm-to-perineum" time from "arm-to-foot" time, it appears that blood flows about twice as fast in the sympathectomized limb as it does in the normal limb.

Table V shows the results in eight individual cases. In a very few instances there was a difference of but one or two seconds, and in one case there was no difference at all. In the great majority of cases, however, the difference was large, and in some instances amounted to eighteen or nineteen seconds. The subjects who noted differences of speed of blood flow to sympathectomized and unsympathectomized legs were firm in their statements that not only was the sensation perceived in the sympathectomized leg much sooner than in the unsympathectomized leg, but that the sensation was likewise more distinct. In several cases in which "blanks" resulted before sympathectomy, the sensation was perceived distinctly after sympathectomy. The average figures of 39.2 seconds to the unsympathectomized foot from the arm, and 25.5 seconds to the unsympathectomized foot from the ventricle, in instances of unilateral sympathectomy, are both greater than the average values in the unsympathectomized extremities in normal subjects,¹ and appear to indi-

TABLE V

CIRCULATION TIMES IN CASES OF ESSENTIAL HYPERTENSION, SHOWING THE RESULTS BEFORE AND AFTER SYMPATHECTOMY

CASE	TIME OF TEST IN RELATION TO SYMPATHECTOMY	TIME IN SECONDS					
		ARM TO TONGUE	ARM TO PERI- NEUM	ARM TO R. HAND	ARM TO L. HAND	ARM TO R. FOOT	ARM TO L. FOOT
1	Preoperative	16	23	24	24	35	35
	9 days after left	16	23	25	31	28	26
	11 days after right	14	24	23	20	29	29
2	Preoperative	11	17	15	15	33	33
	8 days after left	12	19	23	18	31	27
	15 days after right	18	23	28	28	33	33
3	Preoperative	16	24	26	26	54	54
	7 days after right	16	23	28	30	32	50
	11 days after left	15	24	30	36	35	35
4	Preoperative	15	20	23	23	42	42
	7 days after right	13	20	22	24	24	40
	13 days after left	16	24	36	Blank	33	33
5	Preoperative	11	17	20	20	31	31
	8 days after right	12	19	24	24	26	45
	13 days after left	13	16	18	18	20	20
6	Preoperative	17	42	28	27	63	59
	11 days after right	16	30	22	26	33	49
	9 days after left	18	24	28	26	39	36
7	Preoperative	12	17	23	23	45	45
	9 days after right	13	18	17	17	23	23
	14 days after left	10	11	13	13	15	15
8	Preoperative	14	28	21	21	40	47
	18 days after right	12	39	21	26	31	36
	13 days after left	11	23	19	19	30	30

cate diversion of an unusually large amount of blood to the sympathectomized side, with consequent slowing of blood flow on the opposite side.

However, the important point is that sympathectomy of one extremity increases greatly the speed of blood flow in the arteries of that extremity. This increased speed of blood flow seems to be a direct result of vasodilatation produced by sympathectomy. An interesting observation is that in many instances blood flows faster in an extremity when it alone has been sympathectomized, than it does in the same extremity after the companion member has been sympathectomized as part of the second stage of the operation for hypertension (Table V). This may be due to the reduction of blood pressure caused by the second operation. Since the blood pressure has been reduced, blood flows less rapidly because, if the degree of vasodilatation remains roughly constant, the volume of blood flow would be directly proportional to blood pressure.

TABLE VI
ESSENTIAL HYPERTENSION AFTER BILATERAL SYMPATHECTOMY
(THIRTY-SIX TESTS ON TWENTY-THREE SUBJECTS)

TIME IN SECONDS	NUMBER OF TESTS					
	ARM TO TONGUE	ARM TO PERINEUM	ARM TO R. HAND	ARM TO L. HAND	ARM TO R. FOOT	ARM TO L. FOOT
0-4	0	0	0	0	0	0
5-9	0	0	0	0	0	0
10-14	15	1	1	2	0	0
15-19	20	11	5	6	2	2
20-24	1	20	10	9	8	8
25-29	0	4	11	9	11	10
30-34	0	0	4	1	5	8
35-39	0	0	2	4	6	4
40-44	0	0	0	0	2	2
45-49	0	0	1	1	2	2
50-54	0	0	1	0	0	0
Blanks	0	0	1	4	0	0
Mean*	14.88±.28	21.14±.42	26.40±.88	25.03±.90	29.61±.78	29.38±.82
Stan. dev.*	2.53	3.76	7.73	7.52	6.91	7.26

*Time in seconds.

TABLE VII
ESSENTIAL HYPERTENSION AFTER BILATERAL SYMPATHECTOMY
(THIRTY-SIX TESTS ON TWENTY-THREE SUBJECTS)

TIME IN SECONDS	NUMBER OF TESTS				
	VENTRICLE TO PERINEUM	VENTRICLE TO R. HAND	VENTRICLE TO L. HAND	VENTRICLE TO R. FOOT	VENTRICLE TO L. FOOT
0-4	11	2	4	0	0
5-9	22	12	9	9	9
10-14	3	15	13	11	10
15-19	0	3	4	7	11
20-24	0	1	1	7	4
25-29	0	0	1	1	1
30-34	0	2	0	1	1
Blanks	0	1	4	0	0
Mean*	6.25	11.54	10.50	14.72	14.50

*Time in seconds.

It is of interest that in thirty-six tests performed on twenty-three subjects who had undergone bilateral sympathectomy, "blanks" did not occur in the feet (Tables VI and VII). This but demonstrates the importance of adequate vasodilatation in the feet before the sensation of warmth produced by the injected solution can be perceived.

Orthostatic Hypotension.—Following the original observation of Brown and one of us (Adson),¹² and, more recently, those of Roth¹³ and of two of us (Allen and Adson),^{7, 8} that after anterior rhizotomy or bilateral subdiaphragmatic extraperitoneal resection of the splanchnic nerves, celiac ganglia, and the first and second lumbar ganglia, the blood pressure falls and the pulse rate increases when the patient stands, we desired to ascertain what effects, if any, these disturbances had on the circulation time. Five patients with orthostatic hypotension and tachycardia following operation for essential hypertension were studied (Table VIII). The test was first done with the patient in the recumbent position after a rest of half an hour. Within five to ten minutes the patient was allowed to stand, the blood pressure and pulse rate were again taken, and the test was repeated with the arm at the patient's side (Table VIII).

TABLE VIII

CIRCULATION TIME IN CASES OF ORTHOSTATIC HYPOTENSION RESULTING FROM SYMPATHECTOMY FOR HYPERTENSION

CASE	BLOOD PRESSURE	PULSE RATE	POSITION OF BODY	TIME IN SECONDS					
				ARM TO TONGUE	ARM TO PERI-NEUM	ARM TO R. HAND	ARM TO L. HAND	ARM TO R. FOOT	ARM TO L. FOOT
1	180/122	92	Lying	13	21	23	23	27	27
	102/82	128	Standing*	55	61	61	61	71	71
2	156/112	84	Lying	15	20	25	25	31	31
	112/88	124	Standing	29	36	48	48	Blank	Blank
3	152/94	92	Lying	13	17	19	19	25	25
	84/60	128	Standing	16	20	28	28	32	32
4	106/64	100	Lying	13	16	18	18	20	20
	60/40	96	Standing	22	25	31	31	62	62
5	134/84	92	Lying	10	15	17	17	22	22
	74/60	132	Standing	18	30	24	24	48	48

*No reactions at end of 35 seconds. Patient then lay down because of vertigo and faintness, reactions occurring from time of injection.

Two patients with spontaneous orthostatic hypotension were studied, but no reactions occurred within two minutes when the patients were standing, and consequently had marked decreases in blood pressure. Surprisingly, when they lay down again, reactions produced by the injected solution occurred within about the same time after lying down as they did after the moment of injection when the injections were made originally with the patients lying down. These limited observations on spontaneous orthostatic hypotension indicate that the blood was almost entirely stagnant in the veins when these two patients were standing, and explain the marked weakness which prevented their standing more than two or three minutes.

As far as we have been able to determine, the circulation time in orthostatic hypotension has not been extensively studied. Prinzmetal and Wilson,⁴ by the use of the plethysmograph, found no change in the volume flow of blood in the arm in a case of postural hypotension with the patient in either the lying or standing position. The results of our study of orthostatic hypotension resulting from sympathectomy indicate that the "arm-to-tongue," "arm-to-hand," "arm-to-perineum" and "arm-to-foot" times are all prolonged when the patient stands and the blood pressure is reduced (Table VIII). The marked slowing of the circulation in these cases is due to slowing of both venous and arterial circulation. For example, in Case 5, the "arm-to-tongue" time was increased only eight seconds, while the "ventricle-to-foot" time was increased eighteen seconds when the patient stood.* In this instance the speed of blood flow was decreased in both arteries and veins.

CONCLUSIONS

1. The circulation time in cases of essential hypertension falls within normal limits, except that the "arm-to-foot" time is slightly increased. We do not know whether or not this indicates diminished blood flow to the feet in essential hypertension, but the figures suggest such a possibility.

2. Unilateral sympathectomy for hypertension decreases the circulation time from the arm to the sympathectomized foot to a value about nine seconds less than it is to the unsympathectomized foot. After bilateral sympathectomy for hypertension the average "arm-to-foot" circulation time, as determined by thirty-six tests on twenty-three subjects, is about 29.5 seconds, or about three to five seconds faster than normal. This increased speed of flow is attributed directly to vasodilatation.

3. In spontaneous orthostatic hypotension there is a marked increase in the "arm-to-tongue" time and in the "arm-to-foot" time when the patient stands. In orthostatic hypotension which results from extensive sympathectomy for essential hypertension, the decrease in speed of flow of blood occurs in the peripheral veins and pulmonary circulation, as well as in the peripheral arteries.

REFERENCES

1. Kvale, W. F., and Allen, E. V.: The Rate of the Circulation in the Arteries and Veins of Man. I. Studies of Normal Subjects and of Those With Occlusive Arterial Disease and Hyperthyroidism, *AM. HEART J.* 18: 519, 1939.
2. Spier, L. C., Wright, I. S., and Saylor, Leslie: A New Method for Determining the Circulation Time Throughout the Vascular System, *AM. HEART J.* 12: 511, 1936.
3. Pickering, G. W.: The Peripheral Resistance in Persistent Arterial Hypertension, *Clin. Sc.* 2: 209, 1936.
4. Prinzmetal, Myron, and Wilson, Clifford: The Nature of the Peripheral Resistance in Arterial Hypertension With Special Reference to the Vasomotor System, *J. Clin. Investigation* 15: 63, 1936.

*The method of calculating "ventricle-to-foot" time has been described in a previous publication.

5. Steele, J. M., and Kirk, Esben: The Significance of the Vessels of the Skin in Essential Hypertension, *J. Clin. Investigation* 13: 895, 1934.
6. Williams, M. M. D.: Personal communication to the authors.
7. Allen, E. V., and Adson, A. W.: The Physiological Effects of Extensive Sympathectomy for Essential Hypertension, *AM. HEART J.* 14: 415, 1937.
8. Allen, E. V., and Adson, A. W.: Physiologic Effects of Extensive Sympathectomy for Essential Hypertension: Further Observations, *Ann. Int. Med.* 11: 2151, 1938.
9. Brown, G. E.: Calorimetric Studies of the Extremities. III. Clinical Data on Normal and Pathologic Subjects With Localized Vascular Disease, *J. Clin. Investigation* 3: 369, 1926.
10. Herrick, J. F., Essex, H. E., and Baldes, E. J.: The Effect of Lumbar Sympathectomy on the Flow of Blood in the Femoral Artery of the Dog, *Am. J. Physiol.* 101: 213, 1932.
11. Freeman, N. E.: The Effect of Temperature on the Rate of Blood Flow in the Normal and in the Sympathectomized Hand, *Am. J. Physiol.* 113: 384, 1935.
12. Adson, A. W., and Brown, G. E.: Malignant Hypertension: Report of Case Treated by Bilateral Section of Anterior Spinal Nerve Roots From the Sixth Thoracic to the Second Lumbar, Inclusive, *J. A. M. A.* 102: 1115, 1934.
13. Roth, Grace M.: The Postural Effects on Blood Pressure Following Interruption of the Vasomotor Nerves of Man, *AM. HEART J.* 14: 87, 1937.

THE RATE OF THE CIRCULATION IN THE ARTERIES AND VEINS OF MAN

III. THE INFLUENCE OF TEMPERATURE OF THE SKIN, DIGESTION, POSTURE, AND EXERCISE*

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THE study of the effect of physiologic processes on the rate of circulation of blood in man has been limited almost entirely to that in the veins, since there was no suitable method for determining the speed of blood flow in arteries until Kahler¹ described his method in 1929. A similar method was described by Spier, Wright, and Saylor² in 1936. They injected intravenously a solution of calcium, magnesium, and sodium, and determined the time elapsing between injection and the occurrence of a warm sensation in the tongue, perineum, hands, and feet. We have used this method and have reported the results of our studies in normal subjects and in subjects with various pathologic conditions.^{3, 4} As stated in a previous publication, we believe that information regarding speed of flow in arteries can be secured by subtracting the "arm-to-tongue" time from the "arm-to-foot" time, the result being a figure which indicates roughly the "ventricle-to-foot" time, that is, the time required for blood to flow from the left ventricle to the foot. "Ventricle-to-hand" time can be estimated by a similar calculation.

The method we have used permits investigation of the influence of temperature of the skin, digestion, posture, and exercise on the speed of flow of blood in the arteries.

EFFECT OF TEMPERATURE OF THE SKIN ON SPEED OF CIRCULATION

Effect of Environmental Temperature.—The effect of skin temperature on peripheral volume flow of blood was demonstrated by Hewlett and Van Zwaluwenburg,^{5, 6} in 1910, by Stewart,^{7, 8} in 1911, and by Freeman,⁹ in 1935.

In our studies the patient was allowed to remain at rest for at least one hour, or longer, if necessary, until his blood pressure, pulse rate, and skin temperature had attained a basal level. A thermocouple was attached to each great toe and to the third finger of each hand, and the

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Received for publication June 20, 1939.

TABLE I
EFFECT OF SKIN TEMPERATURE ON CIRCULATION TIME

EXP.	PROCEDURE	ROOM TEMP. (° C.)	SKIN TEMPERATURE (° C.)					TIME IN SECONDS							
			R1 TOE	L1 TOE	R3 FINGER	L3 FINGER	ARM TO TONGUE	ARM TO PERINEUM	ARM TO R. HAND	ARM TO L. HAND	ARM TO R. FOOT	ARM TO L. FOOT			
1	Control *	25.0	24.0	25.7	30.3	32.0	12	18	24	22	35	38			
		26.2	33.1	34.7	36.1	36.3	11	16	19	19	25	28			
2	Control † *	25.2	27.2	27.4	30.3	29.7	12	18	22	20	41	37			
		18.8	18.5	18.5	18.7	19.2	14	21	Blank	36	Blank	Blank			
3	Control *	20.0	37.0	37.4	38.8	38.8	11	16	18	17	23	26			
		25.9	25.1	25.2	30.5	29.8	12	17	23	26	42	37			
4	Control † *	26.4	36.5	37.0	37.1	34.9	11	16	17	18	21	22			
		25.2	26.5	26.3	27.4	27.0	17	30	33	37	52	43			
5	Control *	18.8	20.0	20.7	19.5	19.5	17	27	44	Blank	Blank	Blank			
		19.5	38.5	32.6	35.7	37.0	16	25	19	26	39	32			
		23.9	22.7	22.7	20.6†	20.0†	11	14	16	20	28	28			
		23.5	35.2	35.4	36.6	36.6	10	15	12	16	22	23			

*Vasodilatation induced by baker over body.

†Vasoconstriction induced by lowered environmental temperature.

‡Hands placed in ice water at 6° C. for one minute; thirteen minutes before readings were recorded.

temperature of the skin ascertained by means of the Sheard electric thermometer.¹⁰ As soon as the control test had been obtained the patient was transferred to a room the temperature of which was 5 to 7° C. colder (Cases 2 and 4 of Table I). When the patients were subjected to the low environmental temperature, sensations usually provoked by the injected solution were felt only in the left hand (Case 2) and right hand (Case 4), and in both instances the circulation time was increased. As we shall show later, failure to perceive sensation is due to decreased cutaneous temperature.

Effect of Reflexly Induced Vasodilatation.—Vasodilatation was produced by a body baker after a suitable control period, during which a test was performed. Skin temperatures were recorded every minute, and after vasodilatation had occurred the test was repeated (Table I). In every instance, with the exception of the "arm-to-perineum" time in Case 5, the speed of the blood flow was increased. Especially was this so in the case of the feet, and in cases in which "blanks" had occurred with a lowered environmental temperature there were none when sufficient vasodilatation had been produced.

*Explanation of So-Called Blanks.**—The "blanks" which occasionally occurred in this study disturbed us. They were especially frequent in the feet. Some of them were due to confusion on the part of the patient, who would forget to report all regions; in these instances repetition of the test in five to ten minutes might produce the reaction, but there still seemed to be some other factor that played a role in the occurrence of "blanks." This factor was apprehended gradually as more and more tests were done. It was noted that on especially warm days there were relatively few "blanks"; that on cold days and in a cold

TABLE II

EFFECT OF VASODILATATION PRODUCED BY APPLICATION OF EXTERNAL HEAT ON CIRCULATION TIME

(EXPLANATION FOR THE OCCURRENCE OF "BLANKS")

EXPERIMENT	SKIN TEMPERATURE (° C.)		TIME IN SECONDS	
	R ¹ TOE	L ¹ TOE	ARM TO R FOOT	ARM TO L. FOOT
1	23.4	23.4	Blank	Blank
	34.3	35.7	44	44
2	24.3	24.3	Blank	Blank
	40.1	40.4	27	27
3	30.0	28.7	Blank	Blank
	35.0	34.5	32	28
4	24.0	24.2	Blank	Blank
	38.7	38.2	25	25
5	24.0	24.2	Blank	Blank
	35.4	37.7	20	20

*When no sensation is perceived in a foot, for example, after the solution is injected, the result is recorded as "blank."

room they occurred rather frequently. This led to the observation that skin temperature was important in the frequency of occurrence of "blanks." Whenever "blanks" occurred, vasodilatation was induced by direct application of radiant heat to the feet and legs. After suitable warming of the skin, sensation was perceived routinely (Table II).

The tonic state of the arterioles in the feet seems to have more of a bearing on the perception of the sensation than it does in the hands. "Blanks" occur relatively rarely in the hands and perineum, but in the feet they are met with in 19 to 20 per cent of instances. There seem to be two reasons for this. The feet are usually colder than the hands, and the longer circuit to the feet may cause enough dilution of the solution so that a sufficiently high concentration of the solution does not reach them.

Vasodilatation in One Extremity.—Since unilateral sympathectomy causes blood to flow much faster⁴ in the sympathectomized leg than it does in the normal one, we investigated the effect of unilateral vasodilatation induced by heat. The application of external heat to one extremity produces vasodilatation not only in that extremity, but also reflexly in the other extremities. To overcome this reflex vasodilatation, an ordinary blood pressure cuff was placed around the thigh of the leg to which external heat was to be applied, and was inflated to the level of the diastolic pressure in order that the venous return might be obstructed.¹¹ A baker was then placed over the leg until there was a difference in the cutaneous temperature of the two legs of at least 5° C. The cuff was then deflated and the test performed at once. These studies indicate conclusively that an increased cutaneous temperature is associated with increased speed of flow (Table III). However, the difference in temperature of the skin of the two extremities was not proportional to the difference in circulation time.

TABLE III
EFFECT OF VASODILATATION IN ONE LEG ON CIRCULATION TIME

CASE	TEMPERATURE OF SKIN OF TOES (° C.)		ARM-TO-FOOT CIRCULATION TIME (IN SECONDS)	
	RIGHT	LEFT	RIGHT	LEFT
1	29.5	38.0	49	37
2	24.5	31.9	73	51
3	29.4	35.6	47	43
4	27.7	32.8	46	38
5	28.2	34.3	42	30

EFFECT OF TACHYCARDIA ON SPEED OF BLOOD FLOW

Atropine sulfate, in doses of $\frac{1}{50}$ and $\frac{1}{60}$ grain (0.0013 and 0.0011 gm.), administered subcutaneously, induced tachycardia; the maximum occurred from one to two hours after injection (Table IV). Changes

TABLE IV
EFFECT OF TACHYCARDIA ON CIRCULATION TIME*

EXP.	PROCEDURE	PULSE	SKIN TEMPERATURE (° C.)				TIME IN SECONDS							
			R1 TOE	L1 TOE	R3 FINGER	L3 FINGER	ARM TO TONGUE	ARM TO PERINEUM	ARM TO R. HAND	ARM TO L. HAND	ARM TO R. FOOT	ARM TO L. FOOT		
1	Control +	56	23.5	23.5	24.4	24.7	13	18	21	23	30	30	30	
		104	25.7	25.8	30.2	30.4	11	14	17	16	21	21	21	
2	Control +	60	31.6	30.7	32.5	31.7	12	20	22	19	28	28	28	
		96	33.9	33.5	34.7	35.0	12	16	15	14	18	18	18	
3	Control +	60	31.8	31.1	32.0	31.1	10	23	23	23	29	31	31	
		88	30.3	28.6	30.8	31.4	10	20	21	21	25	25	25	
4	Control +	68	26.5	26.2	26.5	25.9	14	27	30	31	39	37	37	
		100	28.4	27.1	28.1	26.5	10	16	23	21	27	27	27	
5	Control +	80	29.7	30.1	32.7	34.0	13	21	22	17	35	39	39	
		96	32.3	31.8	34.0	34.8	14	20	19	19	29	27	27	
6	Control +	80	26.5	27.8	30.0	30.0	13	22	20	20	36	34	34	
		100	26.1	27.4	32.7	34.5	12	22	20	25	34	36	36	

*Experiments carried out in constant-temperature room.

†One to two hours after the subcutaneous injection of atropine sulfate.

in blood pressure were minimal. The temperature of the skin of the fingers and toes usually increased somewhat. If we disregard increase in cutaneous temperature as a cause for changed speed of circulation,* tachycardia induced by atropine increased the speed of flow in all instances except the "arm-to-tongue" time and "arm-to-left-hand" time in experiment 5, the "arm-to-perineum," "arm-to-right-hand," "arm-to-left-hand," and "arm-to-left-foot" time in experiment 6, and the "arm-to-tongue" time in experiments 2 and 3. Blumgart and Weiss¹² also found that the rate of blood flow from arm to arm increased when there were conspicuous increases of the pulse rate.

EFFECT OF EXERCISE ON SPEED OF BLOOD FLOW

Ellis,¹³ in 1932, showed that the arm-to-carotid-sinus circulation time in five cases, computed from his tables, was decreased an average of 6.3 seconds after the subjects had exercised on a bicycle. In our studies the circulation time was first determined with the patient at rest. He then ascended and descended the stairs (described by Master and Oppenheimer¹⁴) for one minute, at the end of which time he was allowed to lie down and the test was immediately repeated. In almost all instances the speed of flow was increased (Table V). Calculations of speed of

TABLE V
EFFECT OF EXERCISE ON CIRCULATION TIME

CASE		PULSE	TIME IN SECONDS					
			ARM TO TONGUE	ARM TO PERI-NEUM	ARM TO R. HAND	ARM TO L. HAND	ARM TO R. FOOT	ARM TO L. FOOT
1	Before exercise	88	10	15	18	17	22	20
	After exercise	140	8	11	14	17	23*	20
2	Before exercise	80	12	18	19	19	31	31
	After exercise	120	9	14	16	17	21	21
3	Before exercise	80	11	16	20	20	26	26
	After exercise	104	4	7	13	13	22	22
4	Before exercise	76	13	26	22	20	47	33
	After exercise	120	11	14	18	18	31	31
5	Before exercise	84	11	14	19	19	41	41
	After exercise	120	11	17*	22*	23*	32	38
6	Before exercise	80	12	18	19	19	31	31
	After exercise	124	9	14	16	17	21	21

*Indicates prolongation, rather than shortening, of circulation time as a result of exercise.

blood flow from "ventricle to foot," as described in a previous communication, indicate that the rate of flow in the peripheral arteries is increased as a result of exercise. Perhaps all of the increased speed of flow is due to increased cardiac output, associated with tachycardia.

*This is not allowable, of course, since previous studies indicate that cutaneous temperature increases speed of flow, but in these studies changes in skin temperature were usually minimal.

TABLE VI
EFFECT OF DIGESTION ON CIRCULATION TIME

EXP.	PROCEDURE	SKIN TEMPERATURE (° C.)				TIME IN SECONDS							
		R ¹ TOE	L ¹ TOE	R ³ FINGER	L ³ FINGER	ARM TO TONGUE	ARM TO PERINEUM	ARM TO R. HAND	ARM TO L. HAND	ARM TO R. FOOT	ARM TO L. FOOT		
1	Control 1 h. 35 m.*	27.6	30.9	32.5	32.7	13	19	22	20	39	31		
		31.0	31.6	34.4	34.8	12	20	20	19	31†	25		
2	Control 2 h. 35 m.*	28.6	29.8	31.3	31.1	12	22	23	23	31	31		
		31.1	32.3	34.5	33.4	11	19	19	16	28	39†		
3	Control 1 h. 58 m.*	31.3	32.0	32.0	33.3	22	30	36	36	51	51		
		32.2	32.6	34.0	34.2	21	29	27	27	46	46		
4	Control 2 h. 20 m.*	29.7	27.3	31.3	32.1	18	26	32	32	46	46		
		32.2	32.8	31.4	32.5	14	22	25	25	35	35		
5	Control 2 h. 45 m.*	28.0	27.2	31.5	31.6	11	14	19	19	41	41		
		31.0	31.2	31.7	31.3	14	20	26	22	38	41		

*After large meal.

†Cuff around leg inflated to the level of diastolic pressure.

EFFECT OF DIGESTION ON SPEED OF BLOOD FLOW

Herrick, Essex, Mann, and Baldes,¹⁵ in 1934, using a thermostromuhr, showed that the volume flow of blood in the carotid, femoral, and mesenteric arteries of dogs was increased during digestion. Their results were confirmed by McCracken, Essex, and Sheard,¹⁶ who injected small quantities of the disintegration products of radon (radium emanation) into the jugular veins of animals and noted the time required for them to pass to a point in the femoral artery lying in the adductor canal. They found that the circulation time in dogs was decreased 12.9 to 45.5 per cent during the course of digestion.

The subjects of our observations were placed in a constant-temperature room, without breakfast, and rested for at least an hour and a half, or until their blood pressure, pulse rate, and skin temperatures were stable. A control circulation time was then obtained. They were then allowed to eat a large breakfast, consisting of orange juice, three fried eggs, bacon, buttered toast, a sweet roll, and milk. The blood pressure, pulse rate, and skin temperatures were then taken as often as seemed necessary. The height of digestion, which was judged by the maximal increase in skin temperature, occurred from an hour and a half to two hours and a half after eating. The blood pressure changed insignificantly, the heart rate increased four to twelve beats per minute in different subjects, and the cutaneous temperatures increased somewhat.

TABLE VII
EFFECT OF POSTURE ON CIRCULATION TIME

CASE		PULSE	TIME IN SECONDS					
			ARM TO TONGUE	ARM TO PERINEUM	ARM TO R. HAND	ARM TO L. HAND	ARM TO R. FOOT	ARM TO L. FOOT
1	Lying	80	13	18	24	24	27	27
	Standing	96	12	17	24	24	29	29
2	Lying	78	12	20	24	23	28	28
	Standing	92	15	24	27	35	49	50
3	Lying	72	14	19	20	23	25	25
	Standing	104	14	19	20	23	31	31
4	Lying	64	12	19	14	17	24	25
	Standing	92	13	18	21	10	31	31
5	Lying	76	10	14	12	17	25	25
	Standing	104	12	19	21	17	29	29
6	Lying	68	15	25	28	28	45	45
	Standing	68	19	25	48	48	Blank	Blank
7	Lying	92	12	16	23	18	31	31
	Standing	100	11	17	18	18	30	30
8	Lying	88	14	19	23	23	33	33
	Standing	96	13	21	23	23	38	38
9	Lying	80	20	27	45	45	51	51
	Standing*	92						
†	†		103	109	Blank	Blank	112	112
	‡		13	19	Blank	Blank	22	22

*No reaction for ninety seconds, lay down with reactions occurring.

†From time of injection.

‡From time of lying down.

The results are given in Table VI. In all experiments, except the fifth, it will be seen that the speed of the blood flow was usually increased as a result of digestion.

EFFECT OF POSTURE ON SPEED OF BLOOD FLOW

The effect of posture on the speed of venous circulation has been fairly well studied,¹⁷⁻²⁰ and the results indicate that the upright posture decreases the rate of venous blood flow. This has been attributed to the effect of gravity.

In our studies, control circulation times were first obtained after the patient had lain for a sufficient length of time to allow his pulse rate to approach a basal level. He was then allowed to stand still for five to ten minutes before the second test was done. The results of the study are shown in Tables VII and VIII. The effect of the upright posture on "arm-to-tongue" time was variable (Table VII). The "arm-to-feet" time was increased, except in Case 7. The "arm-to-hand" time was not consistently changed by the upright posture. Calculation of the "ventricle-to-feet" time, as described previously, indicates regular slowing of the arterial circulation, apparently as a result of vasoconstriction resulting from the upright posture (Table VIII).

TABLE VIII
EFFECT OF POSTURE ON CIRCULATION TIME

CASE		TIME IN SECONDS				
		VENTRICLE TO PERINEUM	VENTRICLE TO R. HAND	VENTRICLE TO L. HAND	VENTRICLE TO R. FOOT	VENTRICLE TO L. FOOT
1	Lying	5	11	11	14	14
	Standing	5	12	12	17	17
2	Lying	8	12	11	16	16
	Standing	9	12	20	34	35
3	Lying	5	6	9	11	11
	Standing	5	6	9	17	17
4	Lying	7	2	5	12	13
	Standing	5	8	6	18	18
5	Lying	4	2	7	15	15
	Standing	7	9	5	17	17
6	Lying	10	13	13	30	30
	Standing	6	29	29	Blank	Blank
7	Lying	4	11	6	19	19
	Standing	6	7	7	19	19
8	Lying	5	9	9	19	19
	Standing	8	10	10	25	25
9	Lying	7	25	25	31	31
	Standing*	†				
		6	Blank	Blank	9	9

*No reaction for ninety seconds, lay down with reactions occurring.

†From time of lying down.

CONCLUSIONS

1. The velocity of the flow of blood in the peripheral arteries of man is dependent on cutaneous temperature. Increasing the temperature

increases speed of flow, and decreasing cutaneous temperature decreases speed of flow.

2. The speed of blood flow is increased during digestion.

3. The speed of circulation to the feet is decreased when a patient stands erect. This is apparently due to vasoconstriction which occurs on standing.

4. Exercise increases speed of circulation.

5. Marked increases in the pulse rate, without affecting the blood pressure significantly, and with little or no effect on the temperature of the skin, increase the velocity of blood flow. Minor variations in the pulse rate seem to have no effect on the velocity of flow.

REFERENCES

1. Kahler, H.: Ueber Veränderungen der Blutumlaufzeit (Ein Beitrag zum Problem der Blutgeschwindigkeit), *Wien. Arch. f. inn. Med.* 19: 1, 1929.
2. Spier, L. C., Wright, I. S., and Saylor, Leslie: A New Method for Determining the Circulation Time Throughout the Vascular System, *AM. HEART J.* 12: 511, 1936.
3. Kvale, W. F., and Allen, E. V.: The Rate of the Circulation in the Arteries and Veins of Man. I. Studies of Normal Subjects and of Those With Occlusive Arterial Disease and Hyperthyroidism, *AM. HEART J.* 18: 519, 1939.
4. Kvale, W. F., Allen, E. V., and Adson, A. W.: The Rate of the Circulation in the Arteries and Veins of Man. II. Studies of Hypertension, Orthostatic Hypotension and of the Effects of Sympathectomy, *AM. HEART J.* 18: 537, 1939.
5. Hewlett, A. W.: The Effect of Room Temperature Upon the Blood Flow in the Arm With a Few Observations on the Effect of Fever, *Heart* 2: 230, 1910-1911.
6. Hewlett, A. W., and Van Zwaluwenburg, J. G.: The Rate of Blood Flow in the Arm, *Heart* 1: 87, 1909-1910.
7. Stewart, G. N.: Studies on the Circulation in Man. I. The Measurement of the Blood Flow in the Hands, *Heart* 3: 33, 1911-1912.
8. Stewart, G. N.: Studies on the Circulation in Man. II. The Effect of Reflex Vasomotor Excitation on the Blood Flow in the Hand, *Heart* 3: 76, 1911-1912.
9. Freeman, N. E.: The Effect of Temperature on the Rate of Blood Flow in the Normal and in the Sympathectomized Hand, *Am. J. Physiol.* 113: 384, 1935.
10. Sheard, Charles: The Electromotive Thermometer: an Instrument and a Method for Measuring Intramural, Intravenous, Superficial and Cavity Temperatures, *Am. J. Clin. Path.* 1: 209, 1931.
11. Fatherree, T. J., and Allen, E. V.: Sympathetic Vasodilator Fibers in the Upper and Lower Extremities: Observations Concerning the Mechanism of Indirect Vasodilatation Induced by Heat, *Arch. Int. Med.* 62: 1015, 1938.
12. Blumgart, H. L., and Weiss, Soma: Studies on the Velocity of Blood Flow: the Velocity of Blood Flow in Normal Resting Individuals and a Critique of the Method Used, *J. Clin. Investigation* 4: 15, 1927.
13. Ellis, L. B.: Circulatory Adjustments to Moderate Exercise in Normal Individuals With Particular Reference to the Interrelation Between the Velocity and Volume of the Blood Flow, *Am. J. Physiol.* 101: 494, 1932.
14. Master, A. M., and Oppenheimer, E. T.: A Simple Exercise Tolerance Test for Circulatory Efficiency With Standard Tables for Normal Individuals, *Am. J. M. Sc.* 177: 223, 1929.

15. Herrick, J. F., Essex, H. E., Mann, F. C., and Baldes, E. J.: The Effect of Digestion on the Blood Flow in Certain Blood Vessels of the Dog, *Am. J. Physiol.* 108: 621, 1934.
16. McCracken, E. C., Essex, H. E., and Sheard, Charles: The Circulation Time of the Blood of Dogs Determined by Ionization (Geiger Counter) Methods: the Effects of Digestion, *AM. HEART J.* 14: 60, 1937.
17. Bock, A. V., Dill, D. B., and Edwards, H. T.: On the Relation of Changes in Blood Velocity and Volume Flow of Blood to Change of Posture, *J. Clin. Investigation* 8: 533, 1930.
18. Field, H., Jr., and Bock, A. V.: Orthopnea and the Effect of Posture Upon the Rate of Blood Flow, *J. Clin. Investigation* 2: 67, 1925.
19. Thompson, W. O., Alper, J. M., and Thompson, Phebe K.: The Effect of Posture Upon the Velocity of Blood Flow in Man, *J. Clin. Investigation* 5: 605, 1928.
20. Youmans, J. B., Akeroyd, J. H., Jr., and Frank, Helen: Changes in the Blood and Circulation With Changes in Posture: the Effect of Exercise and Vaso-dilation, *J. Clin. Investigation* 14: 739, 1935.

THE RATE OF THE CIRCULATION IN THE ARTERIES AND VEINS OF MAN

IV. AN ERROR IN THE SODIUM CYANIDE METHOD OF DETERMINING SPEED OF VENOUS BLOOD FLOW*

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MANY methods have been introduced for studying the rate of circulation of blood. In this study, attention will be directed only toward those methods which have as their signal reaction a characteristic taste in the mouth, and the sodium cyanide method, which causes a sudden deep inspiration by stimulation of the carotid sinus. In other words, the circuit involved includes an arm vein, the right side of the heart, the pulmonary system, the left side of the heart, the aorta, and vessels leading to the carotid sinus and tongue.

In the course of other studies, our attention was directed toward the fact that reports of those methods which utilize as their end point a characteristic taste in the mouth indicated that these methods give shorter circulation times than those reported for a method which depends on stimulation of the carotid sinus, that is, the sodium cyanide method. And yet, the distance to the tongue from an arm vein by way of blood vessels is greater than the distance to the bifurcation of the common carotid artery, which is the site of the carotid sinus. It is, therefore, our purpose in this study to present, by injecting appropriate solutions intravenously, a study of this difference in time required to stimulate the end organs in the tongue and that required to stimulate the carotid sinus.

The normal circulation times, as found by various observers, are given in Table I. In every instance except one,¹ the average "arm-to-carotid" circulation time, as measured by the sodium cyanide method, is greater than the "arm-to-tongue" circulation time determined by any one of the other methods. Wood,² using the decholin method on twenty-five subjects, obtained an average of 13.5 seconds, including the injection time. Using the sodium cyanide method on ten subjects, he obtained an average of 15.7 seconds. Gargill,¹ using the decholin method on fifty normal subjects, obtained an average of 15.9 seconds, not including the injection time of 1 to 2 seconds. Using the sodium cyanide method on fifteen normal subjects, he obtained an average of 15.6 seconds. So far

*Abridgment of thesis submitted by Dr. Kvale to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine.

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Received for publication June 20, 1939.

as we know, Gargill's observations are the only ones in which a close correspondence has been found between the "arm-to-tongue" and "arm-to-carotid sinus" circulation time.

PROCEDURE

The method we have used for measuring the "arm-to-tongue" circulation time has been described previously.³ In brief, it consists in determining the time elapsing between the intravenous injection of a solution containing the salts of magnesium, calcium, and sodium into a vein at the elbow, and the occurrence of a warm sensation at the tongue or throat. To ascertain how closely the sudden gasp produced by the action of sodium cyanide on the carotid sinus synchronizes with the sensation of warmth produced by the action of magnesium, calcium, and sodium on the reactive organs in the tongue, we mixed the solution described with a solution of sodium cyanide, after animal experiments had indicated that such a mixture could be injected safely.

The mixture, which consisted of 7 mg. of sodium cyanide dissolved in 0.5 c.c. of distilled water and 2 c.c. of the solution we have been using for determining speed of circulation, was injected into a vein at the elbow in the usual manner. The time elapsing between the injection and the gasp, and that elapsing between the injection and the perception by the patient of warmth in his mouth were carefully noted.

TABLE I

NORMAL CIRCULATION TIME FROM INJECTION OF SOLUTION INTO A VEIN OF THE ARM TO REACTION PRODUCED BY STIMULATION OF CAROTID SINUS (SODIUM CYANIDE METHOD) OR OF NERVES OF THE TONGUE (OTHER METHODS)

OBSERVERS	YEAR	METHOD	RANGE (SEC.)	AVERAGE (SEC.)
Fishberg, Hitzig and King ⁴	1933	Saccharin	9-16	
Wohl and Ettelson ⁵	1935	Saccharin	7.4-20	13.3
Drennan ⁶	1936	Saccharin	12-18	
Webb, Sheinfeld and Colin ⁷	1936	Saccharin	6-18	10.7
Baer and Slipakoff ⁸	1938	Saccharin	9-16	12.6
Hurst and Brand ⁹	1936	Saccharin	12-16	12.7
Kahler ¹⁰	1929	Calcium chloride	9-15	
Leschke ¹¹	1931	Calcium chloride	9-13	
Berinskaya and Meerzon ¹²	1935	Calcium chloride	10-15	11.5
Goldberg ¹³	1936	Calcium gluconate	10-16	12.5
Spier, Wright and Saylor ¹⁴	1936	Calcium, magnesium and sodium salts	7-22	14.6
Kvale and Allen ³	1939	Calcium, magnesium and sodium salts	9-23	13.7
Baer and Slipakoff ⁸	1938	Calcium gluconate	9-16	12.7
Winternitz, Deutsch and Brüll ¹⁵	1931	Decholin	8-14	
Gargill ¹	1933	Decholin	15-20	15.9*
Tarr, Oppenheimer and Sager ¹⁶	1933	Decholin	10-16	13.0
Wood ²	1936	Decholin	9.5-18	13.5†
Alvarez ¹⁷	1933	Endoidine	12-14	
Neurath ¹⁸	1937	Magnesium sulfate	11-17	
Robb and Weiss ¹⁹	1933	Sodium cyanide	9-21	15.6
Gargill ¹	1933	Sodium cyanide	12.5-18	15.6
Wood ²	1936	Sodium cyanide	13-19.5	15.7
Kopp ²⁰	1936	Sodium cyanide	14-20.5‡	

*Injection time not included.

†Injection time included.

‡Includes range in twelve of fifteen patients. In remaining three cases, circulation time was prolonged, for which adequate reasons were given.

RESULTS

The results of eleven such experiments, performed on four subjects, are shown in Table II. In every instance, the sensation of warmth in the tongue was experienced first, and the gasp appeared as the sensation of warmth was subsiding or had disappeared. The results were unquestionable. The subjects on whom these tests were performed and the individuals observing the experiments were impressed by the constancy with which the sensation of warmth in the mouth preceded the gasp. A mean difference of 3.4 seconds was found, with a range of 1 to 5 seconds. In other words, the sensation of warmth in the tongue appeared, on the average, 3.4 seconds sooner than the sudden gasp.

TABLE II
COMPARISON OF CIRCULATION TIMES FROM ARM TO CAROTID SINUS (SODIUM CYANIDE) AND FROM ARM TO TONGUE

SUBJECT	TIME IN SECONDS	
	ARM TO TONGUE	ARM TO CAROTID SINUS
1	11	14
	13	18
2	15	19
	14	18
3	13	16
	14	19
4	7	11
	11	14
	11	13
	14	17
	13	14
Mean	12.36	15.73

Mean difference 3.37.

COMMENT

Mention has already been made of the circulation times between arm and tongue and arm and carotid sinus, as noted by various observers and by us. Attention has been drawn to the fact that in all reports in the literature except one, the "arm-to-tongue" circulation time has been found to be shorter than the "arm-to-carotid" circulation time. And yet, the solution must traverse a greater distance to reach the mouth than the carotid sinus.

It is probable that the solution of sodium cyanide reaches the bifurcations of the carotid arteries before the solution of magnesium and calcium salts reaches the mouth, since both traverse the same pathway.* Assuming that this is true, there appear to be only two explanations for the longer sodium cyanide time. Either the sodium cyanide stimulates the carotid sinus only when all of it has arrived at the bifurcation of the carotid artery, while the first of the magnesium-calcium solution

*It is highly improbable that the solution of sodium cyanide "lags" in the blood stream while the solution of calcium and magnesium salts flows as fast as the blood.

arriving at the site of stimulation is sufficient to call forth a response, or the reaction time of the pathway affected by the sodium cyanide is longer. It seems unlikely that any two pathways involved, each culminating in a motor response, would show a discrepancy of three seconds in reaction, or traversal, time. It therefore seems probable that a summation effect is required for the sodium cyanide to act on the carotid sinus.

The sodium cyanide method has been recommended because it requires no cooperation on the part of the patient, yet it can now be demonstrated that it is less accurate than the subjective method which we and other investigators have used, as far as determination of circulation time is concerned. We do not wish to minimize the value of the sodium cyanide method, for normal values for it have been established and the error in it seems relatively constant. Hence the method may be used freely for comparative purposes if it is remembered that it has an inherent error. Whatever the explanation, our studies show conclusively that the solution which we have used in our investigations gives more reliable information about the actual speed of flow of blood from an arm to the tongue than sodium cyanide does when used to determine the speed of blood flow from an arm to the carotid sinus.

CONCLUSIONS

By mixing a solution of sodium cyanide with a solution of magnesium, calcium, and sodium salts, and injecting this mixture into a cubital vein, it has been shown that there is an error in the sodium cyanide method of determining speed of blood flow. The time required for blood to flow from an arm vein to the carotid sinuses, as ascertained by injection of a solution of sodium cyanide, appears to be about three seconds more than the time actually required for blood to flow from an arm vein to the carotid sinuses.

REFERENCES

1. Gargill, S. L.: The Use of Sodium Dehydrocholate as a Clinical Test of the Velocity of Blood Flow, *New England J. Med.* 209: 1089, 1933.
2. Wood, Paul: Right and Left Ventricular Failure: a Study of Circulation Time and Venous Blood Pressure, *Lancet* 2: 15, 1936.
3. Kvale, W. F., and Allen, E. V.: The Rate of the Circulation in the Arteries and Veins of Man. I. Studies of Normal Subjects and of Those With Occlusive Arterial Disease and Hyperthyroidism, *AM. HEART J.* 18: 519, 1939.
4. Fishberg, A. M., Hitzig, W. M., and King, F. H.: Measurement of the Circulation Time With Saccharin, *Proc. Soc. Exper. Biol. and Med.* 30: 651, 1933.
5. Wohl, M. G., and Ettelson, L. N.: III. Studies in Obesity: Effect of Dinitrophenol on Blood Velocity, *J. Pharmacol. and Exper. Therap.* 55: 439, 1935.
6. Drennan, L. M., Jr.: The Clinical Significance of the Blood Circulation Time as Determined by the Saccharin Test, *M. Ann. District of Columbia* 5: 238, 1936.
7. Webb, George, Sheinfeld, William, and Colin, Hyman: The Importance in Surgery of the Blood Circulation Time, *Ann. Surg.* 104: 460, 1936.

8. Baer, S., and Slipakoff, B. G.: Measurement of Circulation Times and the Agents Used in Their Determination, *AM. HEART J.* 16: 29, 1938.
9. Hurst, Allan, and Brand, M. A.: A Study of Venous Pressure and Circulation Time in Pulmonary Tuberculosis, *J. Thoracic Surg.* 6: 638, 1937.
10. Kahler, H.: Über Veränderungen der Blutumlaufszeit (ein Beitrag zum Problem der Blutgeschwindigkeit), *Wien. Arch. f. inn. Med.* 19: 1, 1929-1930.
11. Leschke, Erich: Kreislaufzeit und Blutgeschwindigkeit, München. med. Wehnschr. 78: 2117, 1931.
12. Berinskaya, A. N., and Meerzon, T. I.: Determination of Velocity of Circulation in Functional Diagnosis of Circulation, *Klinicheskaya Meditsina*, Moscow 13: 70, 1935. Abstr. in: *J. A. M. A.* 104: 1680, 1935.
13. Goldberg, S. J.: Use of Calcium Gluconate as a Circulation Time Test, *Am. J. M. Sc.* 192: 36, 1936.
14. Spier, L. C., Wright, I. S., and Saylor, Leslie: A New Method for Determining the Circulation Time Throughout the Vascular System, *AM. HEART J.* 12: 511, 1936.
15. Winternitz, M., Deutsch, J., and Brüll, Z.: Eine klinisch brauchbare Bestimmungsmethode der Blutumlaufszeit mittels Decholininjektion, *Med. Klin.* 27: 986, 1931.
16. Tarr, L., Oppenheimer, B. S., and Sager, R. V.: The Circulation Time in Various Clinical Conditions Determined by the Use of Sodium Dehydrocholate, *AM. HEART J.* 8: 766, 1933.
17. Alvarez, C.: El tiempo de circulación y su medida clínica. Empleo de la endoioidina, *Rev. méd. del Rosario.* 23: 595, 1933.
18. Neurath, Otto: Untersuchungen über die Bestimmung der Blutumlaufgeschwindigkeit mit Magnesiumsulfat, *Ztschr. f. klin. Med.* 132: 134, 1937.
19. Robb, G. P., and Weiss, S.: A Method for the Measurement of the Velocity of the Pulmonary and Peripheral Venous Blood Flow in Man, *AM. HEART J.* 8: 650, 1933.
20. Kopp, Israel: The Arm-to-Carotid Circulation Time in Prolonged Therapeutic Fever, *AM. HEART J.* 11: 667, 1936.

ANEURYSM OF THE PULMONARY ARTERY

A REVIEW OF THE LITERATURE AND REPORT OF TWO NEW CASES

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A NEURYSM of the trunk or of the main branches of the pulmonary artery is rare. Among 37,757 consecutive autopsies reviewed by three groups of workers¹⁻³ not a single case was encountered; no examples were observed among 1,671 cases of aneurysm.³⁻⁵ However, Crisp⁶ noted two instances while compiling a series of 530 aneurysms, although he found no record of involvement proximal to the bifurcation of the main trunk. Although the combined studies of Henschen,⁷ D'Aunoy and von Haam,⁸ and Jennes¹ would indicate that 122 cases of aneurysm of the pulmonary artery had been reported up to 1936, exclusion of instances of dilatation of the pulmonary artery and inclusion of cases previously overlooked would raise the number to a total of 139. Up to 1906, in only two cases among forty-six was the correct diagnosis made *ante mortem*,^{9, 10} but progressive improvement in roentgenologic methods has raised the number of correct diagnoses to twelve of the 122 known in 1936, and to twenty-eight at the present time (September, 1939).

If discussion is limited to cases observed since 1833 in which the diagnosis was confirmed by necropsy, 111 examples of aneurysm of the trunk or of one or both main branches are available for analysis. The figure is obtained by using the statistics of D'Aunoy and von Haam⁸ (omitting cases 16 and 76 of their report, since the smaller branches were affected), and adding all other cases reported up to the present time (September, 1939). Dissecting aneurysms not arising as a result of aneurysm, and simple diffuse dilatation, irrespective of cause or size, have been excluded.

The term "pulmonary aneurysm" is here limited to those dilatations which are the result of, or associated with, actual damage to one or more coats of the vessel. Justification for the inclusion of any given case rests on autopsy (Table I) or reasonably positive clinical (Table II) findings.

All of the patients included in the latter group were still living when the cases were reported. The possibility of confusion with some other lesion is therefore not entirely eliminated. However, careful clinical study of these cases has been the means of developing useful criteria for the recognition of disease of the pulmonary artery, and for that reason a collective analysis seems to be warranted.

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Received for publication Feb. 16, 1939.

Age and Sex.—Males (fifty-five patients) and females (fifty-three patients) were equally affected among the 108 patients whose sex was mentioned. This 1:1 ratio is quite in contrast to the ratio of 5.6 males to 1.0 females observed in cases of aortic aneurysm.¹¹ The mean age for the entire series was 37.7 years, of the females 38.7, and of the males 37.2. The extremes of age were four years¹² and eighty-two years;¹³ both of these patients were females, and the lesions were ascribed to congenital malformations.

The age and sex distribution in 108 cases is shown by the following figures:

Age	0 to 19	20 to 29	30 to 39	40 to 49	50 to 59	60 to 69	70 and over	Total
Male	4	14	7	14	12	2	2	55
Female	9	9	12	7	7	1	8	53
Total	13	23	19	21	19	3	10	108

In addition to indicating the equal sex distribution, the figures are striking in another respect. Thirty-four per cent of pulmonary artery aneurysms occur before the age of 30, while only 16 per cent of aortic aneurysms are encountered in this period;¹¹ while the sexes are equally affected in the former, 88 per cent of the latter are noted in males. A similar incidence of pulmonary aneurysm is observed between the ages of 30 and 60 (38 per cent), whereas 63 per cent of aortic aneurysms occur during this period;¹¹ although males are slightly predominant in the former, aortic aneurysm is eleven times more common in males in this age period. Accordingly, the analysis of age and sex incidence suggests that different etiologic, functional, and anatomic factors are operative in the two types of aneurysm.

Location and Type of Aneurysm.—The trunk of the artery was involved in eighty-nine of 111 cases (trunk alone, seventy-five, trunk and both main branches, nine, trunk and left branch, five); these figures support Costa's¹⁴ contention that the trunk is affected in approximately 85 per cent of the cases. Among trunk aneurysms, thirty-six were fusiform, forty-one were saccular, and the form of the remainder was not specified. The location of the aneurysm in the absence of trunk involvement was as follows: both branches, three; right branch, nine; left branch, ten. Since no fusiform aneurysms of the left branch have been reported, saccular aneurysms predominate in the branches (thirteen left, three right). This may account for the observation that left branch aneurysms are seen more commonly than right.¹⁵

Etiology.—The observation that the pulmonary artery is thinner than other vessels of equal caliber, and that the elastic and muscular component of the media, especially along the anterior and lateral walls, is less abundant, have led to a comparison of its structure with that "of a vein."¹⁶ Moreover, the pulmonary artery seems to partake of the high degree of distensibility which characterizes the lung vessels, presumably

TABLE I.
TABULATION OF FINDINGS IN TWENTY-SIX AUTOPSY CASES OF ANEURYSM OF THE PULMONARY ARTERY

NO.	YEAR	AUTHOR	AGE	SEX	MORPHOLOGY	ETIOLOGY	COINCIDENTAL PATHOLOGIC FINDINGS IN CIRCULATORY SYSTEM
1	1884	Triebel ⁴³	50	M	Saccular aneurysm of trunk, size of a filbert.	Sclerosis	Sclerosis pulmonary artery. No dilatation r. ventricle.
2	1863	Touzé ³³	49	M	Fusiform aneurysm of trunk.	?	A. dissected along artery to second branch. Death by rupture.
3	1902	Mantovani ⁴⁴	25	M	Fusiform aneurysm of trunk.	Rheumatic infection; congen. def.	Mitral stenosis. Congenital stenosis pulmonary artery. Rupture of sac.
4	1904	Ekkert ⁴⁵	42	F	Fusiform aneurysm of trunk with thin, sclerotic wall.	Syphilis; sclerosis (?)	Widespread sclerosis pulmonary artery and aorta.
5	1904	Vincenzo ⁴⁶	54	M	Fusiform aneurysm of trunk and both branches.	Syphilis; sclerosis (?) ; cong. def. (?)	Dilatation and sclerosis of aorta. Death by dissection and rupture.
6	1905	Arnheim ⁴⁷	5	M	Fusiform aneurysm of trunk.	Infection	Congen. stenosis pulmonary valve. Pericarditis. Pulmonary tbc.
7	1917	Reimann ⁴⁸	50	F	Fusiform aneurysm of trunk, 18 cm. in circumference.	Syphilis	Syphilitic mesarteritis with multiple pulmonary infarction.
8	1918	Boinet ⁴⁹	--	--	Saccular aneurysm of trunk.	Infection	Aneurysm sigmoid valve of pulmonary artery with endocardial vegetations.
9	1924	Terplan ⁵⁰	55	F	Circumscribed aneurysm of trunk.	Congen. def.; infection	Open ductus arteriosus. Streptococic endocarditis. Polypous thromboendarteritis of stem of pulmonary artery.
10	1927	Laubry and Thomas ²⁹	45	F	Sacciform aneurysm of trunk.	Syphilis	Generalized syphilitic arteritis.
11	1928	Salzer ⁵¹	60	F	Circumscribed, thrombosed aneurysm of rt. main branch.	Syphilis	
12	1930	Plenge ⁵²	40	M	Saccular aneurysm of trunk.	Syphilis	Marked "lipoid," sclerosis pulmonary artery and aorta.
13	1932	Esser ⁵³	25	F	Sacciform aneurysm of trunk.	Congen. def.	"High-grade" hypoplasia entire vascular system. "Cavernous" pulmonary tbc.
14	1933	Käppeli ⁵⁴ and Lüdin ⁵⁵	71	F	Saccular aneurysm of trunk.	Sclerosis	Pulmonary emphysema. Secondary sclerosis pulmonary artery.
15	1933	Karsner ²⁶	28	F	Fusiform aneurysm of trunk.	Syphilis	Mesaortitis with multiple, small, saccular aneurysms.

*Patterned after table of D'Aunoy and von Haam.⁸

16	1934	Joules ⁵⁶	37	F	Fusiform aneurysm of trunk and both branches.	Congen. def.	Hypoplasia of aorta. Interauricular and interventricular septal defects. Open ductus arteriosus.
17	1934	Holst ⁵⁷	28	F	Aneurysm of trunk.	Infection	Hyperthyroidism. Rheumatic pancarditis with adhesive pericarditis.
18	1934	Scott ⁷⁷	48	M	Saccular aneurysm in each main branch.	Syphilis (?); sclerosis (?)	Moderate coarctation of aorta. Calcified plaques on pulmonary valve and artery. Patent ductus arteriosus.
19	1935	Manzini ⁵⁸	30	M	Fusiform aneurysm of right main branch.	Infection	Hypoplasia of aorta. Open foramen ovale. Marked dilatation of right ventricle. Dilatation trunk of pulmonary artery. Malignant endocarditis with vegetations of pulmonic and mitral valves.
20	1936	Botenga (I) ⁵⁹	62	M	Saccular aneurysm of trunk, 8 cm. in diameter.	Sclerosis	Enormous dilatation right ventricle. Widespread sclerosis pulmonary artery and branches.
21	1936	Botenga (II) ⁵⁹	24	F	Fusiform aneurysm of trunk, with narrowed sclerotic branches.	Congen. def.	Enormous dilatation right ventricle; left very small. Congenital sclerosis of pulmonary artery.
22	1937	Chiari (I) ³⁴	52	F	Ovoid aneurysm of right main branch.	Infection	Rheumatic endocarditis with button-hole mitral valve. Widespread thrombosis of pulmonary artery and of aneurysmal sac.
23	1937	Chiari (II) ³⁴	70	F	Spindle-shaped aneurysm of right main branch, size of a fist.	Syphilis; sclerosis	Endocarditis. Stenosis of pulmonary ostium.
24	1938	Gouley (I) ⁴¹	50	M	Saccular aneurysm of right main branch.	Syphilis	Death from bronchopneumonia.
25	1938	Gouley (II) ⁴¹	61	M	Saccular aneurysm of left main branch.	Syphilis	Chronic interstitial fibrosis of lungs. Pulmonary arteriosclerosis. Hypertrophy of right heart. Focal syphilitic lesions in aorta. Wassermann ++. Death from bronchopneumonia.
26	1938	Gouley (III) ⁴¹	70	M	Saccular aneurysm of right main branch.	Syphilis	Classical syphilitic aortitis. Hypertensive heart disease. Dilatation and hypertrophy of both ventricles.

TABLE II

TABULATION OF FINDINGS IN THIRTY CASES IN WHICH A DIAGNOSIS OF ANEURYSM OF THE PULMONARY ARTERY WAS MADE CLINICALLY

NO.	YEAR	AUTHOR	AGE	SEX	LOCATION AND TYPE	ETIOLOGY	ABNORMAL PHYSICAL FINDINGS IN THE CIRCULATORY SYSTEM AND REMARKS
1	1891	Aristoff ⁶⁰	21	M	Saccular aneurysm of trunk.	?	Thrill, pulsation and harsh systolic murmur second left interspace. Heart enlarged to rt.
2	1904	Rosenfeld ⁶¹	--	--	Fusiform aneurysm of trunk.	--	Patent ductus arteriosus.
3	1912	Rak ⁶²	23	M	Aneurysm of trunk.	Congen. def.	The case suggests simple diffuse dilatation without aneurysm.
4	1918	Colesch ⁶³	39	M	Fusiform aneurysm of trunk, extending into both branches.	Congen. def. Syphilis (?)	Rheumatic carditis. Systolic thrill, pulsation, and bruit in second and third interspaces.
5	1923	Conti ⁶⁴	43	F	Aneurysm of trunk.	Infection	Emphysematous chest. Harsh systolic murmur in pulmonary area. Roentgenogram showed lengthening and lateral projection of conus shadow.
6	1924	Butler and Estap ⁶⁵	21	M	Saccular aneurysm of trunk.	?	Followed fall from horse.
7	1921	Hormaeche ⁶⁶	--	M	Aneurysm of pulmonary artery.	Trauma	Pulmonary emphysema and chronic bronchitis. Pulmonic systolic hum.
8	1924	Kranz ⁶⁷	43	M	Aneurysm of trunk.	Congen. def. Syphilis	Bulging third left costal arch, with systolic thrill, pulsation, and murmur.
9	1924	LeConte and Bordet ⁶⁸	54	M	Sacciform aneurysm of trunk.	Sclerosis (?)	Rheumatic fever. Open ductus arteriosus.
10	1929	Balaban and Pokidoff ⁶⁹	41	M	Aneurysm of trunk extending into both branches.	Trauma (?) Syphilis (?)	Dullness, bulging, systolic thrill, pulsation, and systolic murmur, third left interspace. Accentuation second pulmonic sound.
11	1929	Horn ³⁷	23	F	Saccular aneurysm of left main branch.	Congen. def. Infection (?)	Open ductus arteriosus. Bulging, pulsation, and systolic murmur, third left interspace. Accentuation second pulmonic sound.
12	1931	Lexow ⁷⁰	--	--	Aneurysm of trunk extending into left main branch.	Congen. def.	Syphilitic arteritis of pulmonary artery.
13	1931	Rodrigue and Battro ⁷¹	27	F	Aneurysm of trunk.	Congen. def.	Pulmonary syphilitic arteritis. Insufficiency of pulmonary valve. Pain third and fourth left intercostal spaces. Double pulmonic murmur.
14	1931	Vogl ⁷²	52	F	Aneurysm of trunk.	Syphilis	
15	1933	Calandre ⁷³	43	M	Aneurysm of trunk.	Syphilis	
16	1933	Guénard and Caubet ⁷⁴	44	F	Aneurysm of trunk.	Syphilis	

17	1933	Nann, Muscel et al. ⁷⁵	52	M	Saccular aneurysm of trunk.	Syphilis	Retrosternal pain. Question of aortic aneurysm with secondary pulmonary lesion.
18	1934	Borghetti ⁷⁶	35	F	Saccular aneurysm of trunk.	Infection	Rheumatic fever.
19	1934	Holst (II) ⁵⁷	43	M	Aneurysm of trunk extending into both branches.	Infection	Mitral stenosis of rheumatic origin, with secondary lung stasis. Strongly suggests simple dilatation.
20	1934	Holst (IV) ⁵⁷	54	M	Aneurysm of trunk.	Syphilis (?) Sclerosis (?)	Widened aorta. Calcified plaques roentgenographically.
21	1934	Holst (V) ⁵⁷	26	M	Aneurysm of trunk.	--	Dullness, systolic humming murmur, second left interspace.
22	1935	Gonzales ³⁸	39	F	Sacciform aneurysm of left branch.		Diagnosis made roentgenographically.
23	1935	Steiner ²²	37	M	Aneurysm of trunk extending into left branch.	Congen. def.	Infantilism. Pulmonary stenosis believed cause of aneurysm.
24	1936	Fowler ³²	59	M	Aneurysm of trunk.	?	Left upper thorax more prominent than the right. Visible impulse and loud, harsh murmur, second and third left interspaces. Death from rupture.
25	1936	Jennes (I) ¹	47	F	Aneurysmal dilatation of trunk and both branches.	Congen. def.	Findings suggest interventricular septal defect. Pulmonary regurgitation. Prominent upper left chest and widened dullness second interspace.
26	1936	Jennes (II) ¹	--	M	Aneurysmal dilatation trunk and both branches.	Congen. def.	Roentgenologic findings suggest widespread dilatation, entire tree of pulmonary artery. "Hilar dance."
27	1937	Roesler (VI) ²⁸	39	F	Saccular aneurysm left main lower branch 1.8 cm. in diameter.	Infection	Dilatation trunk and main branches of pulmonary artery. "Septic" endocarditis 18 years previously.
28	1937	Roesler (VIII) ²⁸	17	M	Saccular aneurysm of trunk.	Congen. def.	Right main branch pulmonary artery 2.1 cm. in diameter. Other congenital lesions.
29	1939	Boyd and McGavack (I)	42	M	Saccular aneurysm of left branch.	Syphilis	First symptom, profuse hemoptysis. Wassermann 4+. Presence of aneurysm confirmed at operation.
30	1939	Boyd and McGavack (II)	61	M	Saccular aneurysm trunk and left branch.	Syphilis Sclerosis (?)	Onset with chest pain. Wass. 4+. Cardiac conus enlarged, 2-3 interspaces. Prominent third rib. Systolic thrill and murmur in pulmonary area.

because of their low tonus; attention should also be directed to the fact that the pulse pressure in the lesser circulation exceeds the mean pulmonary arterial pressure.

Direct trauma rarely produces pulmonary artery aneurysm. One patient¹⁶ had suffered a crushing injury, and, in two other cases,^{17, 18} distortion of the artery by a contracting cicatrix resulting from gunshot wounds seemed responsible.

Congenital anomalies¹⁹ were present in 66 per cent of the cases, and were deemed important etiologic factors in 43.2 per cent. Unequal division of the truncus arteriosus was evident in at least six, and open ductus arteriosus in twenty-four (23 per cent). Although pulmonary hypertension occurs in cases of patent ductus arteriosus and has been regarded as causative of aneurysm,^{20, 21} patency of this passage is not uncommon without aneurysm. Accordingly, it seems reasonable to assume that some additional lesion, such as superimposed infection or atheromatosis, may contribute to the production of aneurysm in this group.^{3, 7, 20} Pulmonary stenosis (thirteen cases) or insufficiency (two cases) may be present. In Steiner's case,²² infantilism accompanied the cardiovascular anomalies. These lesions may be isolated or accompanied by pulmonary sclerosis. Patency of the interventricular septum increases intrapulmonic pressure and can cause arterial dilatation; it was present four times. Patency of the foramen ovale (eleven cases) was usually associated with more significant lesions (eight cases). Bicuspid and quadricuspid pulmonary valves, mitral stenosis, hypoplasia of the pulmonary artery, hypoplasia of the aorta (5.7 per cent), stenosis of the aorta (6.7 per cent), and aortic coarctation were also encountered.

Nonspecific arteriosclerosis of the pulmonary artery was present and regarded as partly provocative in 23 per cent of the cases.

Although Warthin²³ believed that syphilis was responsible in all of the fifty-one cases^{7, 24} reviewed by him, this view has not remained unchallenged. Peck regarded only twenty-nine cases reported up to 1927 as possibly syphilitic in origin, and in only twelve of these did syphilis seem indisputably related;²⁵ however, Karsner²⁶ has questioned the role of syphilis in three of these twelve. Peck²⁵ also concluded that syphilis attacks the main trunk almost exclusively, and only occasionally extends to major branches. If this view is valid, it makes the old conception of the role of syphilis dubious; syphilis was supposed to affect the minute pulmonary vessels, to induce pulmonary hypertension, and, by concomitant, specific mesopulmonitis, to cause aneurysm. As a matter of fact, in only three of Peck's twenty-nine patients did the macroscopic and microscopic changes in the pulmonary artery aneurysm approximate those customarily seen in aortic aneurysm. However, if the assumption of D'Aunoy and von Haam is valid (twenty-three syphilitic aneurysms among eighty-seven cases), the additions reported since their

paper would raise that figure to thirty-three cases (31.7 per cent). The etiologic role of syphilis is difficult to understand, for the sex distribution is equal, and 88 per cent of the cases of aortic aneurysm, a lesion universally regarded as syphilitic in an overwhelming percentage of the cases, occur in males. Likewise, some doubt has been cast upon the older notion that pulmonary artery aneurysm in young individuals (usually in females) arises from a congenital malformation, and that in the older patients, who are predominantly males, it is caused by syphilis.

In eighteen patients infections other than syphilis seemed responsible; in seven, rheumatic endocarditis, in six, septic endocarditis, and in five, unspecified infection had been superimposed upon a congenital heart lesion.

Clinical Features.—For reconstruction of the clinical picture, twenty-eight cases in which the correct clinical diagnosis was reached have been added to the 111 cases in which the diagnosis was proved by necropsy. Oppenheimer's eight cases of idiopathic dilatation of the pulmonary artery were excluded because they represent congenital vascular anomalies of the artery, rather than aneurysm.²⁷ The cases of Roesler,²⁸ Laubry and Thomas,²⁹ and Taussig et al.,³⁰ are omitted for the same reason. On the other hand, although Jennes³¹ cases may well belong to the same group, they are included because it was inferred from clinical studies that an aneurysm was present. Likewise, the associated pathologic changes or complications may overshadow or mimic the signs in such a way as to preclude the correct diagnosis. Henschen⁷ stated that only four of forty-six cases were "pure."

Some clarification of the clinical picture may be attained by the recognition of two groups of cases: (a) when the trunk is involved, exclusively or in combination; (b) when one or both main branches are affected. In the first form the complete picture of aneurysm of the pulmonary artery, described originally by Baader,³¹ in 1765, may be seen. It is an aneurysm of signs *and* symptoms, whereas that of the branches is an aneurysm of symptoms. Syphilis was present in 29 per cent of the first group and 40 per cent of the second, while congenital lesions were equally distributed (43 per cent in each group).

The subjective symptoms in the two groups are similar. *Palpitation* has been considered the earliest symptom, but is not common (23.8 per cent). *Dyspnea* (76.9 per cent) and *cyanosis* (50.8 per cent) may appear early in cases in which there is an associated congenital malformation, while *pain* (60.5 per cent) and *cough* (78.8 per cent) antedate dyspnea and cyanosis in the absence of a congenital lesion. The dyspnea is often of the exertional type. A sensation of suffocation (4.8 per cent) or of "fullness" (40.3 per cent) in the chest is commonly ascribed to mechanical pressure. *Precordial pain* is not uncommon

(36.5 per cent), and is, at times, related to pericarditis. Shoulder pain with radiation down the arm (11.5 per cent),^{32, 33} and distress in the back³⁴ and in various parts of the chest, associated with thromboses, have been reported. Substernal burning or pain (11.5 per cent) may or may not be due to an associated syphilitic aortitis. Cough (79.0 per cent) may be (a) nonproductive when caused by increased mediastinal pressure acting on the recurrent laryngeal nerve; (b) dry and subsequently productive, from bronchial irritation with or without broncho-stenosis; and (c) productive of bloodstreaked sputum or frank hemorrhage resulting from pulmonary thromboses, often multiple. The first variety is uncommon, and recurrent laryngeal paralysis has not been reported.

Edema is always a late symptom; it is slight, recurrent, and usually limited to the lower extremities, although ascites is not uncommon. Save when syphilis affects a single branch of the artery, pulmonary stasis is constant.

The physical findings have not always been reported. The left side of the chest was more prominent than the right in forty-four of forty-eight cases. This enlargement was definitely localized to the region of the second and third costal cartilages in thirty-two cases, and is ascribed to the proclivity of aneurysm to affect the anterior wall of the vessel. Twice this development has occasioned detachment and necrosis of costal cartilages. A pulsation is observed more commonly in the second left intercostal space than elsewhere (64.5 per cent), and is usually attributed to an associated congenital defect. *Fremitus* in the same area may be either systolic (58.3 per cent) or diastolic (6.2 per cent). A diastolic thrill (12.5 per cent), with or without an associated murmur, usually signifies a complication, such as endocarditis. Dullness in the second left intercostal space (52 per cent) accompanies enlargement of the pulmonary conus and the trunk of the artery, which become applied to the chest wall as they enlarge. Right-sided cardiac enlargement is almost constantly present at autopsy, but it was commonly missed on physical examination (recognized in twelve of forty-eight cases). A systolic murmur may be most clearly audible in the second and third left intercostal spaces (83.3 per cent); usually it has a harsh, sawing, or rubbing character, but lacks a definite line of transmission.

The roentgenologic findings, which have been increasingly helpful in recognizing the lesion, may be summarized as follows:

A. Anterior view.—There is an accentuation of the middle arch, with increase in length and lateral projection. This may assume a globular form, and may pulsate if a thrombus has not formed. Extension to the right of the right heart border is seen in some cases. The left side of the silhouette moves in a "seesaw" manner, with the pulmonary conus

area and the ventricular shadow expanding alternately. In such instances the left border of the heart is formed by the right ventricle only; the left has been rotated dorsad.

B. Right anterior oblique view.—The aneurysmal shadow encroaches upon the retrosternal space, usually presenting a knoblike appearance in the posterior mediastinum below the level of the aortic arch and above the level of the left atrium. Such a picture is seen commonly in cases of dilatation of the right main branch, but a similar effect can occur when the aneurysmal pouch of the trunk develops to the right and in front of the aorta. Indentation of the esophagus below the normal aortic impression may result from direct pressure or transmitted pressure by way of the left bronchus.

C. Left anterior oblique view.—Encroachment upon the ventral and caudad aspects of the aortic window as a result of aneurysms of the trunk and of the left branch will be noticed; less frequently one sees a lesion of the right side.

Differential Diagnosis.—The diagnosis of aneurysm of the pulmonary artery seems justified when the following findings are simultaneously present: Pulmonary stasis, including dyspnea, cyanosis, oppression of the chest, and bloody sputum; prominence of the left side of the chest in the region of the second and third costal cartilages; a pulsation, a thrill, and a loud, superficial, sawing or rubbing systolic murmur in the second left intercostal space; hypertrophy and dilatation of the right side of the heart; a weak apex thrust, with dullness not going beyond the mammary line; lengthening and lateral projection of the pulmonary conus shadow, with the confirmatory roentgenologic signs previously mentioned. The electrocardiogram occasionally shows right axis deviation.

Among the conditions which may be confused with aneurysm of the pulmonary artery are aortic aneurysm, patency of the ductus arteriosus, idiopathic dilatation of the pulmonary artery, and various congenital heart lesions, especially interauricular septal defects. Roentgenologic examination usually distinguishes it from aortic aneurysm. Patency of the ductus arteriosus may be associated with pulmonary artery aneurysm, and a differentiation is impossible when thrombosis exists or when aneurysm of the patent ductus is present.³⁵ The unusually clear and sharply defined hilar pattern, with a comma-like appearance of the descending branch on the right, and the denseness of the large arteries, both in longitudinal views and cross section, are invaluable signs of idiopathic dilatation of the pulmonary artery. Although it may occur in other conditions,²⁸ the so-called "hilar dance"³⁶ is particularly prominent in cases of diffuse dilatation of the pulmonary tree. McGinn and White²⁸ found that an interauricular septal defect was of clinical significance in seven cases; it existed alone in one patient, and in association with patency of the ductus arteriosus in five persons with or with-

out other concomitant anomalies. While the roentgenologic findings in such cases may suggest aneurysm of the pulmonary artery,¹⁸ the absence of murmurs, the right axis deviation, the late cyanosis, and "paradoxical embolism" are helpful in distinguishing the two lesions. The presence of bulging, the type of pulsation, and the thrill and murmur usually serve to differentiate aneurysm of the pulmonary artery from other congenital malformations except patency of the ductus arteriosus.

CASE REPORTS

CASE 1.—A Portuguese, 42 years old, on admission to the hospital July 27, 1937, stated that he had "brought up one quart of blood" ten days before. During the preceding three months his weight had decreased about twelve pounds. For six weeks he had suffered from a dry, hard cough and continuous, dull, occasionally knifelike pain in the back between the shoulder blades, usually referred to the left side, less frequently to the right or to the epigastrium, and aggravated by deepened respiratory movement. Following the hemoptysis he became markedly dyspneic, but this abated gradually during the several days prior to admission.

The patient's *past history* included chicken pox in childhood, "bilious fever" while in Africa in 1912, a middle-ear abscess in 1925, and "gassing" during the World War. He denied venereal infection. He had been married three years, and his wife had had no pregnancies. He had used a package of smoking tobacco daily for the preceding sixteen years and drank wine moderately.

Physical examination disclosed a well-proportioned, fairly well-nourished man, with no palpable enlargement of any of his lymph nodes. His chest was symmetrically developed, with bilaterally equal respiratory expansion. There was slight dullness to percussion posteriorly, extending outward from the root of the left lung. The breath sounds were normal. The heart was normal in size, shape, and position. The blood pressure was 95/60, the pulse rate, 88.

The patient has been continuously followed to date (September, 1939), either in hospital or clinic.

The blood count on several occasions has been always within normal limits. His blood Wassermann, Kahn, and Laughlin reactions have varied from strongly to moderately positive (4 plus to 2 plus) under antisiphilitic therapy. Urinalyses have been essentially negative. The sedimentation rate showed a 4 mm. drop in fifteen minutes, and a 40 mm. decrease at the end of one hour. His blood sugar, nonprotein nitrogen, and creatinine values, in mg. per cent, were 78.0, 31.5, and 1.7, respectively. His sputum has been repeatedly negative for tubercle bacilli. The fractional gastric analysis showed nothing abnormal.

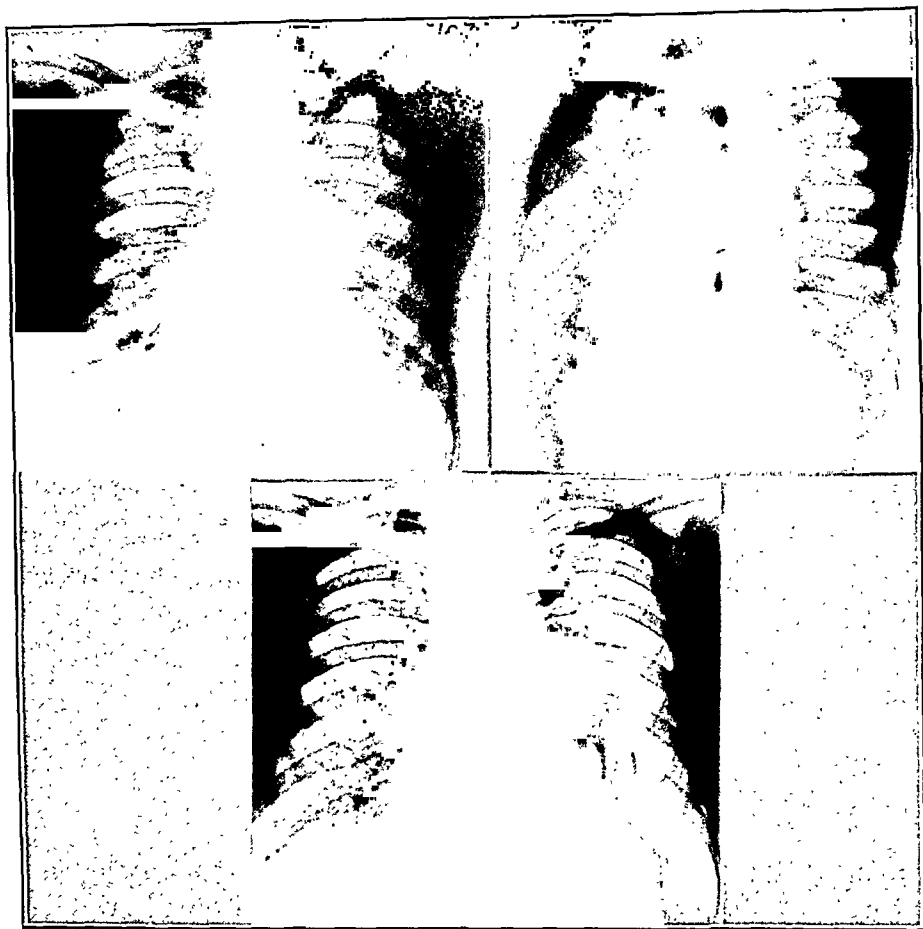
Repeated bronchoscopic examinations revealed some edematous swelling of the aryepiglottic fold, and a smooth, indurated, pale red surface, with three small, circular depressions on the floor and medial wall of the left bronchus immediately below the bifurcation and pointing toward the mediastinum. The consistency of this wall was very firm and immobile. A piece of hard, cheeselike tissue was removed from this area. Histologic examination failed to show any evidence of malignancy or inflammatory change. The electrocardiogram showed no significant changes. There was no right axis deviation.

Frequent roentgenologic examinations (Fig. 1) of the chest in various positions demonstrated a sharply demarcated, nonpulsatile mass in the left hilar region. The periphery of the lung was normal in appearance. Thoracoscopy showed that the mediastinum was entirely free. The structures in the interlobar fissure and peripheral to the hilum were not visualized.

When all findings were considered, it was believed that the patient was suffering from a primary carcinoma in the hilum of the left lung which had not infiltrated peripherally to any appreciable degree. The case was therefore deemed ideal for lobectomy, and on Oct. 19, 1937, this operation was performed under tracheal anesthesia. In the region of the hilum there was a pulsating and expansile aneurysmal mass about the size of a small orange. This aneurysm seemed to extend into the lower lobe and protruded also towards the hilum and immediately posteriorly; it was

A.

B.



C.

Fig. 14, Case 1.—Anteroposterior view, showing very large shadow, extending from the left pulmonary conus, which had no expansile pulsation.

Fig. 1B, Case 1.—Right oblique view. Note the large aneurysmal shadow between the aortic arch and the left atrium.

Fig. 1C, Case 1.—Anteroposterior view following artificial pneumothorax, more sharply outlining the aneurysm of the trunk and left branch of the pulmonary artery.

completely frozen and adherent to the first part of the descending aorta. The attachments to the aorta were so intimate that no line of cleavage could be found. It was decided, therefore, not to attempt any type of surgical treatment of the aneurysm or its sac. The question whether it was an unusual form of aortic aneurysm was raised. At a later date, roentgenologic visualization of the heart and great vessel areas by the method of Robb and Steinberg⁷⁹ demonstrated conclusively that the aneurysm was located on the left main branch of the pulmonary artery.

Following thoracotomy the patient's course was relatively uneventful. The artificially produced pneumothorax disappeared within reasonable time, but the

patient's pain persisted to such an extent that paravertebral injections of alcohol, from the third to the ninth dorsal nerves, inclusive, were finally resorted to on Nov. 18, 1937, and repeated Nov. 30, 1937, in the region of the seventh and ninth roots.

His chest pain, still present on discharge from the hospital Dec. 1, 1937, did not entirely subside until late in February, 1938, since which time he has been reasonably asymptomatic. To date, Sept. 5, 1939, he has had the following antisyphilitic treatment: mercuric salicylate, one injection, 0.015 gm.; bismuth subsalicylate, 60 injections, 1 c.c. each; potassium iodide, 45 minims three times daily for three periods of approximately one month each, and sodium iodide intravenously, 2 gm. three times weekly for a period of two months.

The patient has shown gradual, constant improvement, and presents no complaints at the present time. Both his dry, harassing cough and his chest pain have completely disappeared. Roentgenograms show no appreciable change in the size of the shadow cast by the aneurysm. There are no cardiac changes secondary to the aneurysm.

COMMENT

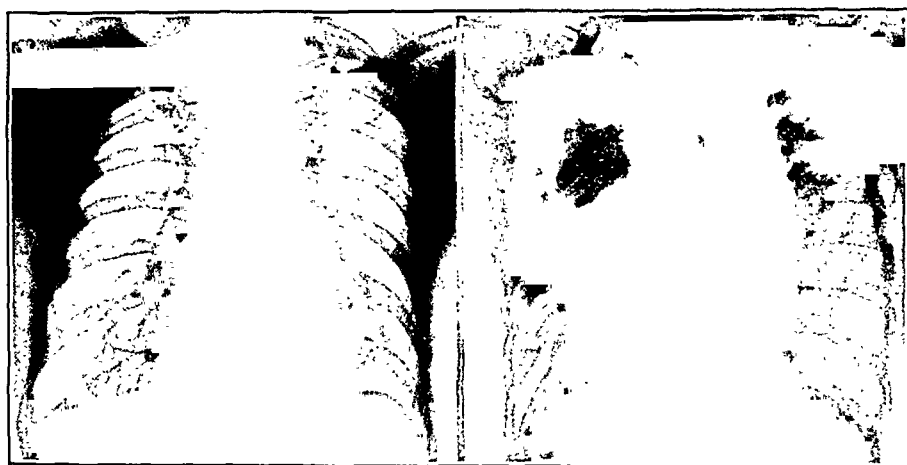
A lesion confined entirely to the left branch of the pulmonary artery with autopsy confirmation of the diagnosis has been observed in eleven cases. The diagnosis has been made clinically in two others.^{37, 38} Operation for presumed tumor of the lung has been performed in one other case,³⁹ in which, however, the lesion involved the trunk as well as both branches of the artery. Hemoptysis as the first symptom of syphilis of the pulmonary artery has been stressed by Brenner⁴⁰ and by Laubry and Thomas,²⁹ who described two such cases. In these the symptoms were secondary to small multiple thrombi which, in turn, were ascribed to a diffuse syphilitic arteritis. Karsner²⁶ found thrombosis in seven of eleven cases of syphilis of the pulmonary artery. The long course which our patient has had, with the marked improvement under antisyphilitic medication, would suggest a similar origin for his initial manifestation, hemoptysis. Our Case 1 proves to be an exception to Peck's²³ statement concerning the location of syphilis in the pulmonary artery. Moreover, there is reasonable proof that nine of the twenty-five aneurysms mentioned as affecting one of the main branches of the pulmonary artery were of syphilitic origin. The operative findings, the positive Wassermann, and the response to antisyphilitic therapy leave little doubt as to the character of the sacular lesion in the foregoing case.

CASE 2.—A 61-year-old white man, nine months before admission to the hospital on June 1, 1938, noticed severe pain in the upper left chest, with radiation to the angle of the scapula on that side. He gave no history of immediately preceding strain or infection and had been able to pursue his occupation as a painter until the onset of the pain.

His *past history* was essentially negative; in particular, there was nothing which might suggest either congenital or acquired heart disease.

Physical examination revealed a well-developed and well-nourished man who had marked hardening of all visible and palpable peripheral arteries. His area of cardiac

dullness was enlarged in the second and third intercostal spaces to the left. Definite prominence of the left third rib and of the second and third intercostal spaces, with marked pulsation in the latter, was noted. A marked systolic thrill was felt in this area, and a loud, harsh, but low-pitched, systolic murmur could be heard. The blood pressure was approximately 130/75 in both arms, and the heart rate was 92. The blood Wassermann was strongly positive (4 plus). His electrocardiogram revealed right axis deviation. The main deflection was slurred in all leads except Lead II. T was very low in Lead I, very high in Lead III, and inverted in Lead IV. The teleroentgenogram (Fig. 2) showed a dilated conus arteriosus, with a semilunar shadow the size of a peach or small apple superimposed upon it and extending into the left lung field. The aorta could be distinctly separated from this shadow throughout its entire course. There were calcified plaques along the right border and over the pulmonic curve of the heart.



A.

B.

Fig. 2A, Case 2.—Anteroposterior view, showing the rounded shadow extending out from an already prominent pulmonary conus.

Fig. 2B, Case 2.—Right oblique view, showing aneurysmal dilatation of the pulmonary conus and extension of the aneurysm along the left pulmonary branch.

COMMENT

In view of the positive Wassermann, the absence of preceding heart disease, and the apparent rapidity with which the lesion developed, syphilis would appear to be the most likely etiologic factor in this case. While the patient's age was above the average, it must be remembered that Gouley⁴¹ has seen three cases, in which syphilis was proved to be the cause of the aneurysm, occurring in individuals between the ages of 59 and 70. The oldest autopsied patient whose lesions were considered to be syphilitic was a woman 75 years of age.⁴² In six of thirty-three reported cases of syphilitic aneurysm in which an autopsy was performed the patients were over 60 years of age. An underlying congenital defect seems unlikely in the present instance, although Weischer¹² found patency of the ductus arteriosus and congenital aortic stenosis in a woman, 62 years old, who had previously shown no evidence of congenital heart disease. The calcified plaques demonstrated roentgenologically in Case 2 could have occurred as a secondary result of either syphilis or pure arteriosclerosis.

The age, mode of onset, clinical course, and physical and roentgenologic findings were in sharp contrast to those in Case 1. The mode of onset resembled that seen by Fowler,³² and, as in his case, there was no previous history of heart disease.

In the two cases described in the present report, the aneurysms were similar only in that apparently they were both of spirochetal origin. Otherwise, on the one hand we have an aneurysm of symptoms with the lesion completely localized to a branch of the artery, and, on the other, involvement of the trunk of the vessel with its accompanying diagnostic group of symptoms and physical signs.

SUMMARY

1. A statistical survey has been made of the clinical and pathologic features of 111 cases of aneurysm of the pulmonary artery in which the diagnosis was confirmed by autopsy.

2. Some of the features of thirty cases in which a clinical diagnosis of aneurysm of the pulmonary artery was made have been summarized.

3. Two cases of aneurysm of the pulmonary artery are reported.

REFERENCES

1. Jennes, Sidney W.: Diffuse Aneurysmal Dilatation of the Pulmonary Artery and Both of Its Branches, *Bull. Johns Hopkins Hosp.* 59: 133, 1936.
2. Moench, G. L.: Aneurysmal Dilatation of the Pulmonary Artery With Patent Ductus Arteriosus, *J. A. M. A.* 82: 1672, 1924.
3. Scott, Ronald B.: Aneurysm of the Pulmonary Artery, With Report of a Case, *Lancet* 1: 567, 1934.
4. Lucke, B., and Rea, M. H.: Studies on Aneurysms. I. General Statistical Data on Aneurysm, *J. A. M. A.* 77: 935, 1921.
5. Klotz, D.: Concerning Aneurysms, Third Gordon Bell Memorial Lecture, April 1, 1926.
6. Crisp, E.: Structure, Diseases and Injuries of the Blood Vessels, London, 1847, p. 90-94, John Churchill.
7. Henschen, S. E.: Das Aneurysma Arteriae Pulmonalis, *Samml. klin. Vort., N.F.*, No. 422-423, 1906.
8. D'Aunoy, R., and von Haam, E.: Aneurysm of Pulmonary Artery With Patent Ductus Arteriosus (Botallo's Duct); Report of 2 Cases and Review of Literature, *J. Path. & Bact.* 38: 39, 1934.
9. Borgherini, A.: Ueber einige Affektionen des Herzgefäßbündels, *Wien. med. Wehnschr.* 46: 1761, 1812, 1856, 1898, 1946, 2086, 2137, 1896.
10. Gilewski: Aneurysma Arteriae pulmonalis, *Wien. med. Wehnschr.* 18: 525, 541, 557, 576, 592, 605, 1868.
11. Boyd, L. J.: A Study of 4000 Reported Cases of Aneurysm of the Thoracic Aorta, *Am. J. Med. Sci.* 168: 654, 1924.
12. Weischer, P.: Ueber die Aneurysmen der Arteria pulmonalis, Würzburg, 1904.
13. Sutherland, G. A.: Congenital Aneurysm of Pulmonary Artery, *Brit. J. Child. Dis.* 27: 8, 1925.
14. Costa, A.: Morfologia e patogenesi degli aneurismi dell'arteria pulmonare, *Arch. di pat. e clin. med.* 8: 257, 1929.
15. Loveland, B. C.: Aneurism of the Pulmonary Artery With Report of Case, *Med. Rec. N. Y.* 39: 349, 1901.
16. Hope, J.: A Treatise on Diseases of the Heart and Great Vessels, London, 1831, W. Kidd.
17. Marble, H. C., and White, P. D.: A Case of Traumatic Aneurysm of the Pulmonary Artery, *J. A. M. A.* 74: 1778, 1920.
18. Castex, M. R., di Cio, A. V., and Battro, A.: Anéurisme de la branche droite de l'artère pulmonaire, *Arch. med.-chir. de l'app. respir.* 6: 303, 1931.

19. Assman, H.: Die klinische Röntgendiagnostik, Leipzig, 1929, p. 159, Vogel.
20. Buchwald: Aneurysma des Stammes der Arteria pulmonalis, Deutsche med. Wehnschr. 4: 1, 13, 25, 1878.
21. Krzyskowski, J.: Aneurysma des Stammes der Pulmonar-arterie und multiple Aneurysmen ihrer Verästelungen bei Persistenz des Ductus Botalli; anatomischer Theil, Wien. klin. Wehnschr. 15: 92, 1902.
22. Steiner, G.: Über das "Aneurysma der Arteria pulmonalis," Röntgenpraxis 7: 168, 1935.
23. Warthin, A. S.: Syphilis of the Pulmonary Artery; Syphilitic Aneurysm of Left Upper Division; Demonstration of Spirocheta Pallida in Wall of Artery and Aneurysmal Sac, Am. J. Syph. 1: 693, 1917.
24. Posselt, A.: Die Erkrankungen der Lungenschlagader, Ergeb. d. allg. Path. u. path. Anat. 8: 298, 1909.
25. Peck, S. M.: Pathologic Anatomy of Syphilis of the Pulmonary Artery; Report of a Case and Review of the Literature, Arch. Path. and Lab. Med. 4: 365, 1927.
26. Karsner, Howard T.: Productive-Cicatricial Syphilitic Disease of the Pulmonary Artery, Arch. Int. Med. 51: 367, 1933.
27. Oppenheimer, B. S.: Idiopathic Dilatation of Pulmonary Artery, Tr. Assoc. Am. Physicians 48: 290, 1933.
28. Roesler, Hugo: Clinical Roentgenology of the Cardio-Vascular System, Baltimore, Ed. 1, 1936, C. C. Thomas.
29. Laubry, C., and Thomas, M.: Les formes anatom-cliniques des artérites pulmonaires chez les syphilitiques, Bull. Soc. med. des Hôpitaux de Paris 51: 9, 1927.
30. Taussig, H. B., Harvey, A. M., and Follis, R. H., Jr.: The Clinical and Pathologic Findings in Interauricular Septal Defects, Bull. Johns Hopkins Hosp. 63: 61, Aug., 1938.
31. Baader, J.: Observ. medic. incision. cadav. anat. illustr., Friburg, 1765.
32. Fowler, W. M.: A Case of Aneurysm of the Pulmonary Artery, AM. HEART J. 11: 370, 1936.
33. Touzé: Une hémorrhagie interstitielle et disséquante des parois de l'artère pulmonaire, accompagnée d'ulcération de ce vaisseau et hémorrhagie dans le péricarde, Bull. Soc. Anat., Paris 38: 13, 1863.
34. Chiari, H.: Zur Kenntnis der Aneurysmen der grossen Lungenschlagaderäste, Wien. klin. Wehnschr. 50: 692, 1937.
35. Lissauer, M.: Ueber das Aneurysma am Stamme der Pulmonalarteria, Virchows Arch. f. path. Anat. 180: 462, 1905.
36. Pezzi, C., and Silingardi, S.: A propos d'un cas d'ectasie de l'artère pulmonaire avec insuffisance de l'appareil valvulaire; signe radio-scopique d'insuffisance pulmonaire, Bull. Soc. méd. Hôp. de Paris 49: 117, 1925.
37. Horn, L.: Zur Kasuistik der Aneurysmen der Pulmonalarterien, Ztschr. f. Kreislaufforsch. 21: 249, 1929.
38. Gonzalez, Sabathié L.: Aneurisma de la rama izquierda de la arteria pulmonar, Rev. Argent. de cardiología. 2: 117, 1935.
39. Wahl, H. R., and Gard, R. L.: Aneurism of the Pulmonary Artery, Surg., Gynec. and Obst. 52: 1129, 1931.
40. Brenner, O.: Pathology of the Vessels of the Pulmonary Circulation, Arch. Int. Med. 56: 1189, 1935.
41. Gouley, Benjamin A.: Personal correspondence.
42. Storch, E.: Ueber zwei Fälle von Lungenarterienaneurysma, Breslau, 1899.
43. Triebel, E.: De Aneurysmate in Umversum adjuncta de arteriae pulmonalis aneurysmate narratione, Inaugural Thesis, Friedrich Academy of "Halensi," Saxony, 1854.
44. Mantovani, G.: Sopra un caso rarissimo do aneurisma del tronco unico dell'arteria polmonare, Torino, 1902.
45. Ekkert, A. F.: Aneurysm of the Pulmonary Artery, Russk. Vrach, 1904, pp. 1237-1241.
46. Vincenzo, G.: Le aeterazioni e gli aneurismi dell'arteria polmonare; casuistica propria; un caso singolare di aneurisma dissecante del tronco unico di tale arteria apertosi nel pericardio, Policlin. 11: 24, 1904.
47. Arnheim, G.: Ein Fall von angeborener Pulmonalstenose, sowie Bemerkungen über die Diagnose des offenen Ductus Botalli, Berl. klin. Wehnschr. 42: 206, 1905.
48. Reimann, S. P.: Aneurysm of the Pulmonary Artery, Proc. Path. Soc. Phila. 22: 42, 1919.

49. Boinet: Anévrisme d'une valvule sigmoïde de l'artère pulmonaire, *Marseille med.* 55: 115, 1918.
50. Terplan, K.: Mykotisches Aneurysma des Stammes der Pulmonalarterie mit Endarteritis des offenen Ductus Botalli mit einem Falle von Endocarditis lenta, *Med. Klin.* 20: 1331, 1924.
51. Salzer, G.: Ueber zwei Fälle von eitriger Entzündung der Lungenschlagader, *Centralbl. f. allg. Path. u. path. Anat.* 41: 100, 1928.
52. Plenge, K.: Zur Frage der Syphilis der Lungenschlagader, *Virchows Arch. f. path. Anat.* 275: 572, 1930.
53. Esser, A.: Seltene Formen von Aneurysmen, *Ztschr. f. Kreislaufforsch.* 24: 737, 1932.
54. Käppeli, A.: Über einen Fall von Aneurysma der Pulmonalarteria, *Ztschr. f. klin. med.* 123: 603, 1933.
55. Lüdin, M.: Aneurysma der Arteria pulmonalis, *Acta radiol.* 14: 259, 1933.
56. Joules, H.: Aneurysmal Dilatation of the Pulmonary Artery in a Case of Congenital Heart Disease, *Lancet* 2: 1338, 1934.
57. Holst, L.: Die Erweiterung des Pulmonalbogens im Röntgenbilde (4 Fälle von Aneurysma der Pulmonalarterie), *Fortschr. a. d. Geb. d. Röntgenstrahlen* 50: 349, 1934.
58. Manzini, C.: Sulla patogenesi della dilatazione del tronco comune della arteria polmonare nell'a stenosi pure, *Cuore e circolaz.* 19: 670, 1935.
59. Botenga, S. P.: Beteekenis van den pulmonalisboog, aneurysma of dilatatie van de longslagader, *Nederl. tijdschr. v. geneesk.* 80: 1460, 1936.
60. Aristoff, V. F.: Case of Aneurysm of the Pulmonary Artery, *Med. Pribav. k. Morskomu Sbornku* 2: 367-439, 1891.
61. Rosenfeld: Zur Diagnostik der Aneurysmen der Arteria pulmonalis, *Fortschr. a. d. Geb. d. Röntgenstrahlen* 8: 290, 1904.
62. Rak, E.: Offener Ductus Botalli mit aneurysmatischer Erweiterung der Arteria pulmonalis, *Wien. med. Wchnschr.* 62: 1128, 1912.
63. Coleschi, L.: Un raro caso di dilatazione dell'arteria polmonare constatato ai raggi X, *Riforma med.* 34: 706, 1918.
64. Conti, P.: Un caso di aneurisma del tronco della polmonare, *Usp. maggiore Milano* 11: 39, 1923.
65. Butler, C., and Estape, J. M.: Dilatation of Pulmonary Artery, *Rev. méd. del Uruguay* 27: 333, 1924.
66. Hormaeche, P.: Aneurysm of Pulmonary Artery, *Rev. méd. del Uruguay* 27: 316, 1924.
67. Kranz, H.: Ueber einen Fall von pulmonal Aneurysma, *Klin. Wchnschr.* 3: 232, 1924.
68. LeConte, M., and Bordet, E.: Dilatation anévristmatique de l'artère pulmonaire, *Bull. et Mém. Soc. méd. de hôp. de Paris* 48: 353, 1924.
69. Balaban, I. Y., and Pokidoff, M. I.: Zur Diagnostik der Aneurysmen der Lungenarterie, *Röntgenpraxis* 1: 454, 1929.
70. Lexow, R.: Angeborenes Aneurysma der Arteria pulmonalis (Stamm und linker unterer Ast), *Ztschr. f. Kreislaufforsch.* 23: 409, 1931.
71. Rodriqué, C., and Battro, A.: Persistencia aneurismática del canal arterial y dilatación aneurismática de la arteria pulmonar, *Prensa méd. argent.* 18: 986, 1931.
72. Vogl, A.: Ein Fall von luischem Aneurysma der Arteria pulmonalis, *Med. Klin.* 27: 1352, 1931.
73. Calandre, L.: Aneurisma de la arteria pulmonar, *Arch. cardiol. y hemat.* 14: 441, 1933.
74. Guénard, F., and Caubet: Un cas d'anévrisme du tronc de l'artère pulmonaire avec insuffisance des valvules pulmonaires, *Arch. d. mal. du coeur* 26: 261, 1933.
75. Nanu, Muscel I., Lazeanu, E., and Stoichita, N.: Sur un cas d'anévrisme de l'artère pulmonaire, *Arch. d. mal. du coeur* 26: 140, 1933.
76. Borghetti, U.: Su di un caso di aneurisma dell'arteria polmonare, *Riforma med.* 50: 1075, 1934.
77. Scott, R. B.: Aneurysm of the Pulmonary Artery, With Report of a Case, *Lancet* 1: 567, 1934.
78. McGinn, S., and White, P. D.: Progress in Recognition of Congenital Heart Disease, *New England J. Med.* 214: 763, 1936.
79. Robb, G. L., and Steinberg, I.: Visualization of Chambers of the Heart, Pulmonary Circulation, and Great Blood Vessels in Man; Practical Method, *Am. J. Roentgenol.* 41: 1, 1939.

CARDIAC METASTASIS FROM MALIGNANT MELANOMA

REPORT OF FOUR CASES

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METASTATIC tumors of the heart are rare. Nicholls¹ tabulated the figures given by a number of authors and found that of a total of 36,980 autopsy cases of carcinoma there were metastases to the heart in 109, or 0.29 per cent. Scott and Garvin² report that in a series of 11,100 consecutive autopsies performed at the Cleveland City Hospital there were 1,082 cases of malignant disease; the heart, including the pericardium, was involved by metastatic tumor in 118 cases, an incidence of 10.9 per cent. Among these cases there were ten malignant melanomas, five of which metastasized to the heart. Lymburner³ states that from 1915 to 1931, in a series of 8,550 autopsies at the Mayo Clinic, there were thirty-six secondary carcinomas and sixteen secondary sarcomas of the heart; six of the tumors were pigmented. Stout,⁴ in his book on cancer, states that at the Presbyterian Hospital of New York one primary and fifteen secondary tumors of the heart were found in a series of 1,171 autopsies over a period of ten years; no mention is made of melanotic tumors. Chayka,⁵ in 1937, reported five cases of cardiac metastasis, none of which was melanoma.

A complete review of the literature reveals reports of only twenty-three cases of malignant melanoma with cardiac metastasis. Here we present four additional cases of cardiac metastasis from malignant melanoma which were observed in the Saint Louis University group of hospitals.

CASE 1.—Mrs. M. V., 30 years of age, had had a pigmented nevus removed from the posterior aspect of the right calf seven months earlier. On physical examination the lungs and heart were negative. A scarred area was found on the posterior surface of the right calf, with small, pigmented nevi surrounding it. In the right femoral region there was a hard mass, 5 cm. in diameter, which was slightly tender, reddened, could not be reduced, and was fixed to the surrounding tissues. Enlarged lymph nodes were palpable around the mass. Biopsy revealed that the tumor was a melanocarcinoma.

At autopsy the body was found to be well developed, but showed some evidence of recent emaciation. Nothing remarkable was noted on examination of the head, neck, chest, and abdomen. In the right calf, near the popliteal fossa, there was a scarred area, the site of a previous cauterization of a pigmented mole. The pericardial cavity was normal in size and contained about 20 c.c. of straw-colored fluid; the serosa lining it was smooth and glistening throughout. The exterior of the pericardium was studded with small white nodules ranging from the size of a pinhead to that of a dime. The heart was about three-fourths the normal size, and its

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Received for publication April 13, 1939.

musculature was rather flabby. The epicardial surface was smooth and glistening. The left ventricle was slightly enlarged. In the endocardium of the left ventricle there was a small grayish mass about 4 mm. in diameter. There was nothing remarkable about the aortic, tricuspid, or pulmonary valves. The edges of the mitral valve were only moderately thickened.

On microscopic examination, the heart muscle was found to be the seat of advanced albuminous degeneration with moderate fragmentation and segmentation of the fibers and some interstitial scarring. Just underneath the endocardium there was a metastatic nodule of carcinoma cells of the pigmented type, most of which were polyhedral and contained a small amount of pigment (Fig. 1).

The anatomic diagnosis was malignant melanoma of the skin of the right popliteal fossa, with metastases to heart, lungs, liver, kidneys, and inguinal and iliac lymph nodes.

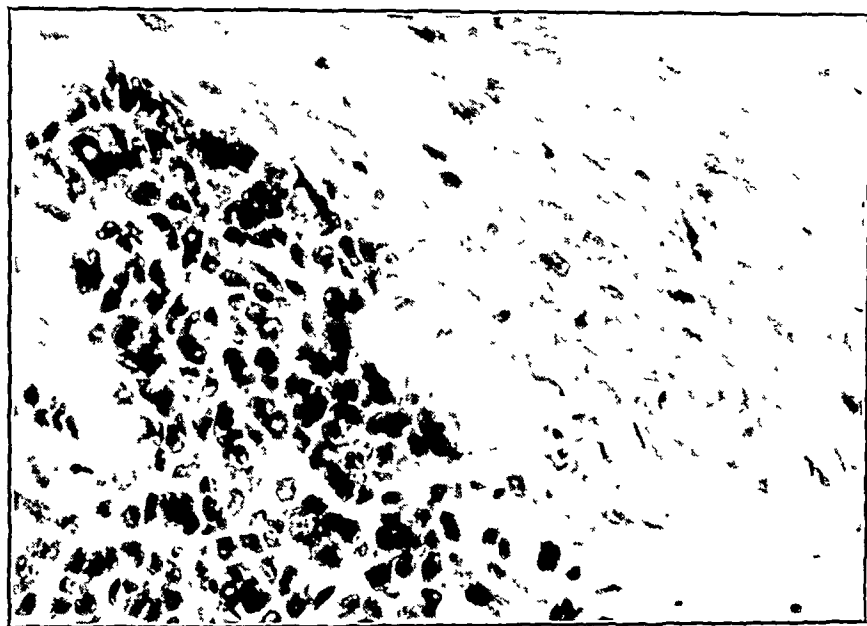


Fig. 1, Case 1.—The tumor cells are polyhedral and contain a small amount of pigment.

CASE 2.—Mrs. S. L. A. was 69 years of age. About five months earlier she had had a melanotic whitlow on the right thumb, which was incised. A short time after the incision the finger became painful, and a tumor appeared and rapidly increased in size. The mass was incised again, and, after roentgen therapy, it had been decided, two and a half months before admission, to amputate the right thumb. Since that time the patient had had marked weakness and loss of appetite, together with pain or discomfort throughout the body resulting from numerous small nodules which appeared in the skin. Examination of the lungs disclosed decreased intensity of the breath sounds in the right upper lobe. Examination of the heart showed nothing abnormal. A mass measuring about four by six inches was palpable in the epigastrium. There were numerous subcutaneous nodules over the back and abdomen, and especially in the axillae.

At autopsy the body was cachectic. Throughout the skin there were many nodules of various sizes and shapes, rounded, and raised above the surface, with a dark bluish or purplish discoloration. These nodules were most numerous about the chest, shoulders, and abdomen. They were less prominent on the extremities, but some could be found even in the scalp. In the mandible in the region of the right canine tooth, which was missing, there was a medium-sized tumor nodule of soft consistency and

a bluish color. The pericardial cavity contained about 4 c.c. of a thin, clear, yellowish fluid. The heart was of average size; its epicardial surface was studded with dark nodules of various sizes, resembling those on the skin. The coronary arteries were slightly tortuous and thickened with fibrous tissue. All of the valve leaflets were thin and filmy. The myocardium was riddled with numerous nodules of the same kind as those mentioned above.

On microscopic examination, the muscle fibers were pale, granular, and degenerated. Spread in between the muscle fibers there were numerous clusters of metastatic tumor cells, most of which were necrotic and degenerated. Many of these tumor cells contained considerable quantities of a golden-brown pigment. Most of the cells were spindle-shaped and did not show any particular arrangement; they had invaded the myocardium extensively (Fig. 2).

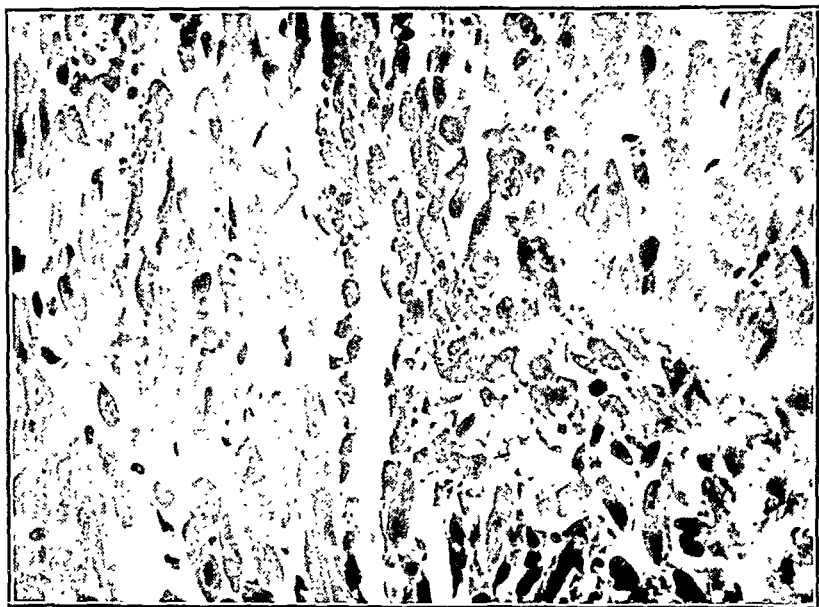


Fig. 2, Case 2.—The tumor cells are mainly spindle-shaped and contain much pigment.

The anatomic diagnosis was malignant melanoma of the right thumb (sub-ungual), with metastases to heart, lung, aorta, liver, intestine, pancreas, kidney, and adrenal.

CASE 3.—Mr. J. Q., a white man, forty-four years of age, had begun to notice numbness and paresthesia on the left side of the body and in upper legs and arms about seven or eight months previously. He had had severe cramps in the calves of both legs. Three weeks before admission he began having headaches (frontal and occipital) which increased in severity and were accompanied by nausea and vomiting. His vision was poor, and he had diplopia. At rest, the right palpebral fissure was narrower than the left. Ophthalmoscopic examination showed blurring of the disc margins, with papilledema, and congestion of the veins of the fundus of the right eye. The fundus of the left eye was normal. The neck and chest were normal. The abdomen was tender to pressure, and there was muscular rigidity in the right upper quadrant and right flank. There were no palpable masses. Neurological examination showed that the patient was confused and disoriented. Examination of cranial nerves 1, 3, 4, 5, 6, 8, 9, 10, 11, and 12 showed nothing abnormal. Vision in right eye (O.D.V.) was reduced to 20/40; vision in the left eye (O.S.V.) was normal, 20/15. There was weakness of the lower facial muscles on the right side. Although the patient was right handed, his gripping power was less on the right than on the left.

The finger-to-nose test showed that there was proximal afferent ataxia in the right arm. The abdominal reflexes were active and equal. The patellar reflexes were equal and normal. The heel-to-toe test showed that sense of position was unimpaired in the lower extremities. The urine was clear, acid in reaction, and contained neither albumin nor sugar. The erythrocyte count was 4,630,000, the hemoglobin 12.5 gm., and the leucocyte count 9,200. The blood Wassermann and Kahn reactions were negative. The nonprotein nitrogen content of the blood was 30 mg. per cent, and the blood sugar value 96 mg. per cent. The spinal fluid was clear, but contained 70 lymphocytes per c. mm.; the Queckenstedt test was positive. The patient was operated on for brain tumor. The immediate postoperative condition was fair, but the day before death his condition changed for the worse.



Fig. 3, Case 3.—The arrows point to metastatic nodules of melanoma in the myocardium.

At autopsy the body was that of a well-developed, poorly nourished white man who appeared older than he really was. Rigor mortis had set in. Hypostatic congestion was present. There was edema of the entire scalp. Two recent wounds were found in the right occipital region. The left sclera and conjunctiva showed evidence of hemorrhage; the right were normal. The pupils were slightly dilated, and equal. The neck, chest, and abdomen were negative. The pericardial cavity contained about 5 c.c. of a greenish-yellow fluid. The heart was of normal size, but the walls were slightly thinned. There were four small, black, flat, smooth tumor growths, about $\frac{1}{2}$ cm. in diameter, in the myocardium of the left ventricle. There was slight thickening of the wall of the aorta. The coronary vessels were normal. The valve leaflets were thin, filmy, and intact. The epicardium was normal throughout. In the mediastinum there were several small tumor nodules, the largest of which measured $3\frac{1}{2}$ to 4 cm. in diameter. The brain contained a large number of round, black, metastatic nodules which varied from $\frac{1}{2}$ to about 4 cm. in diameter. The largest nodule, about 4 to 5 cm. in diameter, was present in the right temporo-occipital region.

Microscopic examination of sections taken from the heart muscle showed a marked degree of edema and congestion throughout, some increase in segmentation and fragmentation of the muscle fibers, and a moderate degree of brown atrophy of the myocardium. In the section there was a large, metastatic nodule formed by large, epithelial-like cells which were polyhedral and contained much brown pigment inside

the cytoplasm (Fig. 4). This pigment proved to be melanin, and the nodule was a metastatic melanoma. Different sections taken from the brain showed multiple metastatic nodules of melanoma, consisting of large, epithelial-like, hyperchromatic cells laden with brown pigment which did not give the Prussian blue reaction. Most of the cells were atypical, grew irregularly, and showed many mitotic figures.

The anatomic diagnosis was malignant melanoma, with metastases to lungs, heart, brain, liver, stomach, both kidneys, bladder, and omentum; the primary growth was most probably in the medulla of the left adrenal.

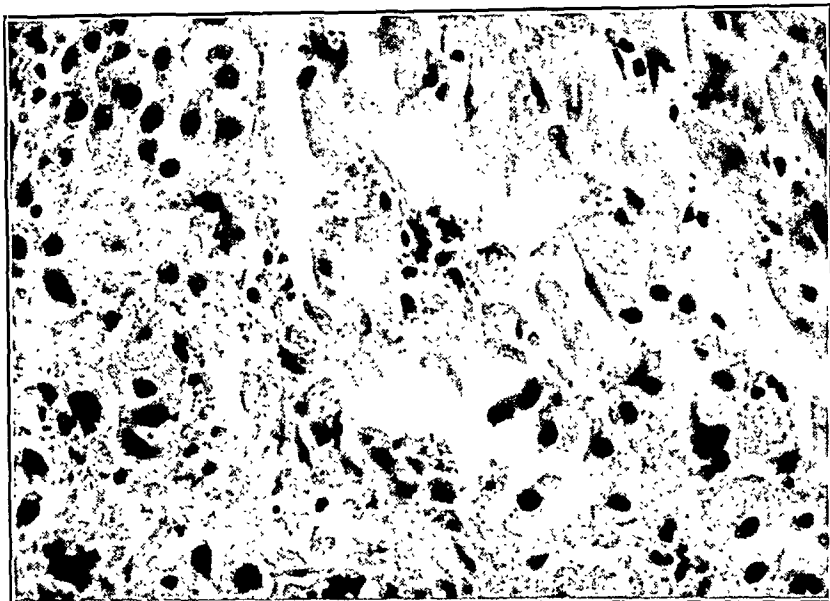


Fig. 4, Case 3.—The tumor cells are for the most part polyhedral and contain much pigment.

CASE 4.—Mrs. S. S. was a colored woman, 39 years of age, who walked into the hospital on June 25, 1938. She complained of severe pain in the left side of the head of two years' duration. She also complained of numerous tender and enlarged lymph nodes which were distributed over the entire body. The patient had had a small tumorlike mass removed from the left parietal region about one year before. The operative wound had been slow to heal. She had received roentgen therapy. Examination revealed a well-developed and well-nourished woman, lying in bed in some distress. On the left side of the head there was an old operative scar, the result of the extirpation of the tumor mass mentioned above. There was increased intraocular tension in both eyes, and at times the sight was impaired. The pupils reacted slowly to light and in accommodation. There were several large, firm lymph nodes in the anterior cervical region; similar masses were also present in the chest. A loud systolic murmur was heard at the mitral and pulmonary areas. The abdomen was normal in contour; several enlarged lymph nodes were felt and seen over this area, and especially in both inguinal regions. An enlarged lymph node was present in the popliteal fossa on the right side. Biopsy revealed that the tumor was a melanosarcoma. The blood pressure was 130/70; the blood Wassermann and Kahn reactions were negative; the erythrocyte count was 3,990,000; the hemoglobin 75 per cent; the leucocyte count 5,350. The urine was clear, acid in reaction, yellow, and the specific gravity was 1.020; it contained slight traces of albumin, but no sugar. There were occasional erythrocytes and leucocytes in the urine. The patient was readmitted to the hospital on Sept. 13, 1938, complaining of abdominal disten-

tion and multiple growths on the abdomen and neck. A paracentesis was performed, and about 1,600 c.c. of reddish ascitic fluid removed. The patient grew steadily worse.

At autopsy the body was emaciated. There was a small scar in the left parietal region, and the hair was missing in this area. A few small, dark nodules were seen on the left upper eyelid. The nose and ears were normal. There were some other black nodules on the face. Examination of the neck revealed many rounded masses of a dark purplish color on both sides, but mainly on the left. These were large lymph nodes. There were also palpable masses in both supraclavicular regions and both axillae. There were many dark nodules of different sizes scattered throughout the chest wall, the abdominal wall, and lower extremities. There was a large, black, metastatic nodule at the margins of the anus, and another on the right buttock. The pericardial cavity was completely obliterated by fibrous adhesions, and somewhat decreased in size because of the small size of the heart itself. On the epicardium there were several small, black, round nodules, and a large calcified plaque on the

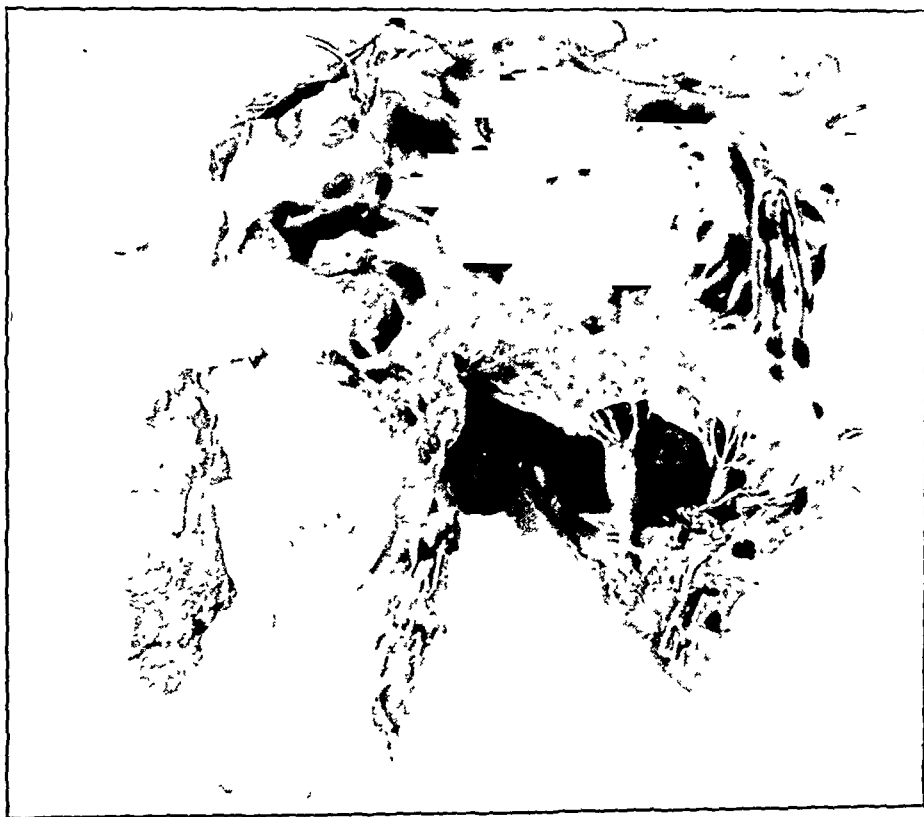


Fig. 5, Case 4.—Multiple metastatic nodules of melanoma in the right atrium and right ventricle.

left ventricle posteriorly. In opening the heart in the usual way, we could see large, black, metastatic masses in the right atrium. In cutting through the tricuspid valve we found numerous metastatic nodules, quite black, in the right ventricle, and there was a fairly large mass of this same black tumor underneath the leaflets of the tricuspid valve affecting the myocardium of the right ventricle (Fig. 5). There was a large pedunculated tumor attached in the region of the conus arteriosus, growing into and almost completely plugging the pulmonary orifice (Figs. 6 and 7). In opening the left atrium and left ventricle we could see some metastatic nodules of melanoma. The myocardium itself showed some small, black nodules spread throughout, between the muscle fibers. The consistency of the muscle was somewhat soft and atonic.

No gross pathologic findings were seen on the heart valves themselves. The aorta showed a moderate degree of atherosclerosis. There was a large, rounded tumor in the lower lobe of the right lung. On section, this mass was black and soft. On the wall of the stomach there were several black tumor nodules; the largest, measuring about 2 cm. in diameter, had ulcerated the gastric mucosa. Throughout the small and large intestine, omentum, and mesentery there were multiple black tumor nodules. In the pelvis, and progressing toward the right lower quadrant, there was a very large black tumor measuring about 10 by 15 cm.; this mass was located on



Fig. 6, Case 4.—Large pedunculated tumors in the right ventricle, in the region of the conus arteriosus.



Fig. 7, Case 4.—Large tumor causing almost complete occlusion of the pulmonary orifice (the patient had a loud systolic murmur in the pulmonary area).

the right side of the pelvis in the region of the right ovary, which could not be found. Several metastatic nodules were found in the liver, pancreas, right kidney, and bladder.

On microscopic examination, the sections of the heart showed a marked congestion throughout. There was also increased fragmentation and segmentation of the muscle fibers, and brown atrophy of the myocardium. Spread throughout the section there were two or three metastatic nodules formed by large, hyperchromatic, atypical cells, most of which were spindle-shaped, and laden with large amounts of granules of a dark brown pigment (Fig. 8). The pigment was melanin, and the cells were those of metastatic nodules of malignant melanoma. The coronary vessels were not particularly thick.

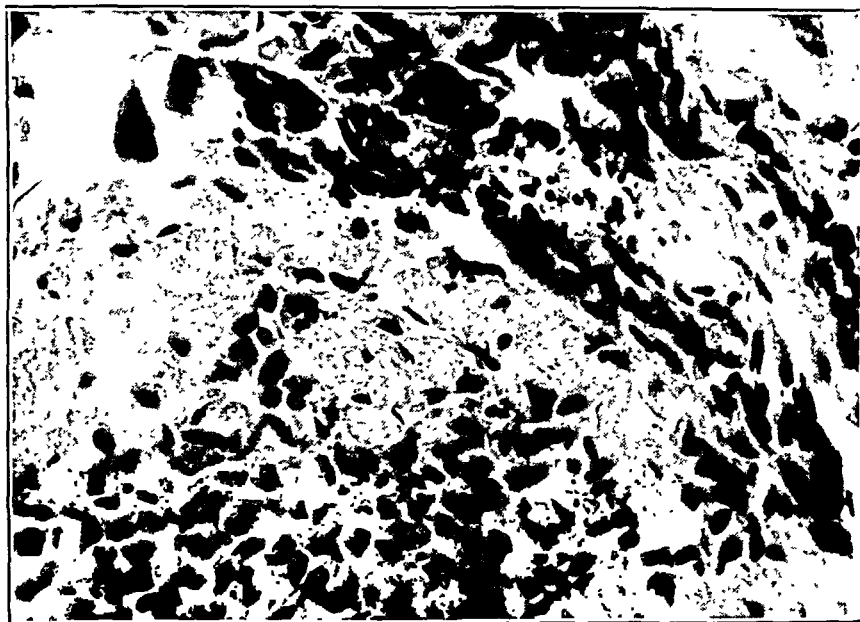


Fig. 8, Case 4.—Most of the tumor cells are spindle-shaped and contain much pigment.

The anatomic diagnosis was malignant melanoma, primary in the scalp, with multiple nodules in the skin and lymph nodes; large metastases to the heart; metastasis to lungs, liver, stomach, pancreas, intestine, and abdominal wall.

COMMENT

We feel strongly that malignant melanoma is one of the tumors which show a relatively common tendency to invade the heart. In Scott and Garvin's series of cases there were ten melanomas, five of which metastasized to the heart (50 per cent); in our autopsy records there were seven cases, in four of which cardiac metastases occurred (57 per cent). The cases found in the literature are the following: In 1903, Delhern and Laignel-Levastine⁶ reported a case of melanotic sarcoma with metastasis in the heart. Goldstein⁷ mentions that Prudhomme, in 1867, reported a case of malignant melanoma with cardiac metastasis in a man; that Erkes, in 1910, reported a diffuse melanosarcoma of the heart; and that Napp refers to two cases of melanosarcoma of the heart described by Deguy. Goldstein also reports three cases of his own. One was that of a melanotic sarcoma which probably started in the right

eye; in the second case there was also a melanotic sarcoma with marked involvement of the adrenals and retroperitoneal and mesenteric lymph nodes; in the third case the tumor originated in a pigmented, soft mole of the labium majus. Lisa,⁸ in 1923, reported the case of a man, 42 years of age, who had a black mole on the upper jaw; it started growing fast, in spite of radium treatment, and soon involved the cervical lymph nodes; numerous subcutaneous masses also developed over the entire body. The autopsy revealed metastasis to heart, lungs, trachea, liver, spleen, kidney, pancreas, stomach, large and small intestine, omentum, and ribs. Yater,⁹ in 1931, described a case of melanosarcoma of the left eye in a man 64 years of age; there were metastases to the brain, heart, lungs, omentum, colon, and pancreas. Burke,¹⁰ in 1934, reported two cases. The first was that of a white woman, 56 years of age, who, a year and a half before death, had a pigmented mole removed from the right wrist by fulguration, followed by roentgen therapy. The lymph nodes in the right axilla and right supraclavicular region became involved soon afterward. The autopsy revealed malignant melanoma, with metastasis to heart, ribs, adrenal, spleen, liver, lungs, kidney, and axillary, mediastinal, and retroperitoneal lymph nodes. Burke's second case was that of a 46-year-old man who had a black wart removed from his back nine months before death. All of the lymph nodes soon became involved, and the autopsy revealed a malignant melanoma which had metastasized to heart, omentum, pancreas, lungs, liver, and adrenals. Lymburner says that in 8,550 autopsies at the Mayo Clinic, from 1915 to 1931, there were six cases of malignant melanoma with cardiac metastasis; in four of the cases the tumor was primary in the skin, and in two, in the eye. In Scott and Garvin's² series of 11,100 consecutive autopsies at the Cleveland City Hospital, there were five cases of malignant melanoma with metastasis to the heart. Among 3,600 autopsies performed in the Saint Louis University hospitals, there were seven cases of malignant melanoma, in four of which cardiac metastasis had occurred.

In most of the cases the involvement of the heart was not suspected clinically. In one of the cases reported by Scott and Garvin, the patient had attacks of paroxysmal auricular fibrillation, and the possibility of cardiac metastasis was considered. In only one of our cases were there any signs that the heart was involved; in this case there was a loud systolic murmur in the pulmonary area caused by a large tumor mass which almost completely occluded the pulmonary orifice. In most of the reported cases the patients were white; melanomas in the negro are very rare. Bauer,¹¹ in 1926, in a review of the literature, could find only fourteen reported cases of malignant melanomas in negroes; he did not include melanotic orbital tumors. One of our cases was in a negress; the cardiac metastases in this case were larger than in the other three cases reported here.

SUMMARY

1. Four cases of cardiac metastasis from malignant melanoma are reported.

2. A review of the literature discloses only twenty-three such cases. Doubtless others have been reported, but under the heading of carcinoma or sarcoma.

3. We believe that cardiac metastasis in cases of malignant melanoma is more frequent than the paucity of reported cases would lead one to think.

4. In one of our cases the patient was a negress, and this is the first time such an occurrence has been reported in that race.

5. In none of the cases presented here was the involvement of the heart suspected clinically.

REFERENCES

1. Nicholls, A. F.: Secondary Carcinoma Implanted on the Endocardium of the Right Ventricle, *Canada M. A. J.* 17: 798, 1927.
2. Scott, R. W., and Garvin, C. F.: Tumors of the Heart and Pericardium, *AM. HEART J.* 17: 431, 1939.
3. Lymburner, R. M.: Tumors of the Heart: Histopathological and Clinical Study, *Canada M. A. J.* 30: 368, 1934.
4. Stout, A. P.: *Human Cancer*, 1932, Lea and Febiger.
5. Chayka, E. I.: Tumor Metastasis in the Heart, *Medichniy Zhurnal*, 8: 1383, 1937.
6. Delhern and Laignel-Levastine: Un cas de sarcome melanique (sarcome secondaire du coeur), *Bull. Soc. Anat. de Paris*, 78: 125, 1903.
7. Goldstein, H. I.: Tumors of the Heart; With Report of Ten Cases, *New York Med. Jour.* 115: 97, 1922.
8. Lisa, J. R.: Three Cases of Metastatic Neoplasms of the Heart, *Proc. New York Path. Soc.* 23: 78, 1923-24.
9. Yater, W. M.: Tumors of the Heart and Pericardium, *Arch. Int. Med.* 48: 627, 1931.
10. Burke, E. M.: Metastatic Tumors of the Heart, *Am. J. Cancer* 20: 33, 1934.
11. Bauer, J. T.: Malignant Melanotic Tumors in the Negro, *Bull. of the Ayer Clin. Lab. of the Pennsylvania Hosp.* No. 10, Dec., 1926.

Department of Clinical Reports

ARTERIOVENOUS FISTULA OF THE LUNG ASSOCIATED WITH POLYCYTHEMIA VERA: REPORT OF A CASE IN WHICH THE DIAGNOSIS WAS MADE CLINICALLY

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SEARCH of the available literature has failed to disclose a case of arteriovenous fistula of the lung in which the diagnosis was made clinically.

REPORT OF A CASE

A man, 40 years of age when first observed at the Mayo Clinic in 1932, related that he had been a "blue baby," small and frail at birth. He continued to be small and underweight until he reached the age of 9 years, when he began to grow rapidly. Through boyhood he played actively and enjoyed apparently good health.

The patient entered the United States Army in 1916, at the age of 24 years. The medical officer who examined him on his enlistment was the first physician to call his attention to the fact that he was cyanotic and that his fingers were clubbed. No abnormal condition of his heart was found at that time. In 1917 he had severe influenza and pneumonia but recovered completely. Thereafter he enjoyed moderately good health until 1924, when, at a time of considerable stress, he suddenly became generally tense, then weak, and finally dropped to the floor. This attack, in which he did not lose consciousness, lasted about thirty minutes. He never had another similar attack.

For a few years before the patient first came to the clinic he had had attacks characterized by invisible tremor of the body, a sensation of fullness in the head, transient tinnitus and vertigo, and tension in the muscles of the back of the neck. Diplopia occurred in one of these attacks. He also had noticed numbness, without tingling, of the hands and feet, slight dyspnea on exertion, and distress in the precordium. During the attacks, he reported, his pulse rate occasionally increased from a normal of 60 to 130 per minute. His systolic blood pressure varied between 90 and 100 mm. of mercury. In the eight years before we first saw him, examination of his blood had disclosed 5,000,000 to 6,000,000 erythrocytes per c.mm. He related that his skin always had been dark.

When the man first was examined at the clinic he weighed 116 pounds (53 kg.) and was short and asthenic. His skin, lips, nail beds, and mucous membranes were cyanotic, and clubbing of his fingers and toes was noteworthy. The blood pressure was 88/52. The pulse rate was 56, and the temperature, 98.4° F. Urinalysis gave negative results. The blood, which was of increased volume, contained 20.6 gm. of hemoglobin per 100 c.c.; the erythrocytes varied from 5,440,000 to 6,220,000 per c.mm., and the leucocytes numbered 3,200 per c.mm. The spleen was not palpable.

The diagnosis was atypical polycythemia vera, treatment for which consisted of venesection, followed by administration of phenylhydrazine. It was believed that

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Received for publication April 26, 1939.

the polycythemia had developed following the influenza and pneumonia fifteen years before, at which time also there may have been a pulmonary abscess.

The patient returned to the clinic in April, 1938. Since his previous visit he had undergone varied treatment. Numerous venesections had afforded him temporary relief. After a course of these, a small capsule of phenylhydrazine had been given to him twice a day. He had taken benzol for a month, but this had had little or no effect. In the latter part of 1935 he had noticed a "hot spot" in his left shoulder. Consciousness of this had been followed by a sense of constriction in the thorax, and, within four hours, he had scarcely been able to breathe. Consequently, he had been taken to a hospital, and oxygen had been administered. He remembered little of the next two weeks but had had considerable pain. Gradually he recovered from this attack. In December, 1936, because of weakness and shortness of breath, he had entered a Chicago hospital, where a small capsule of phenylhydrazine

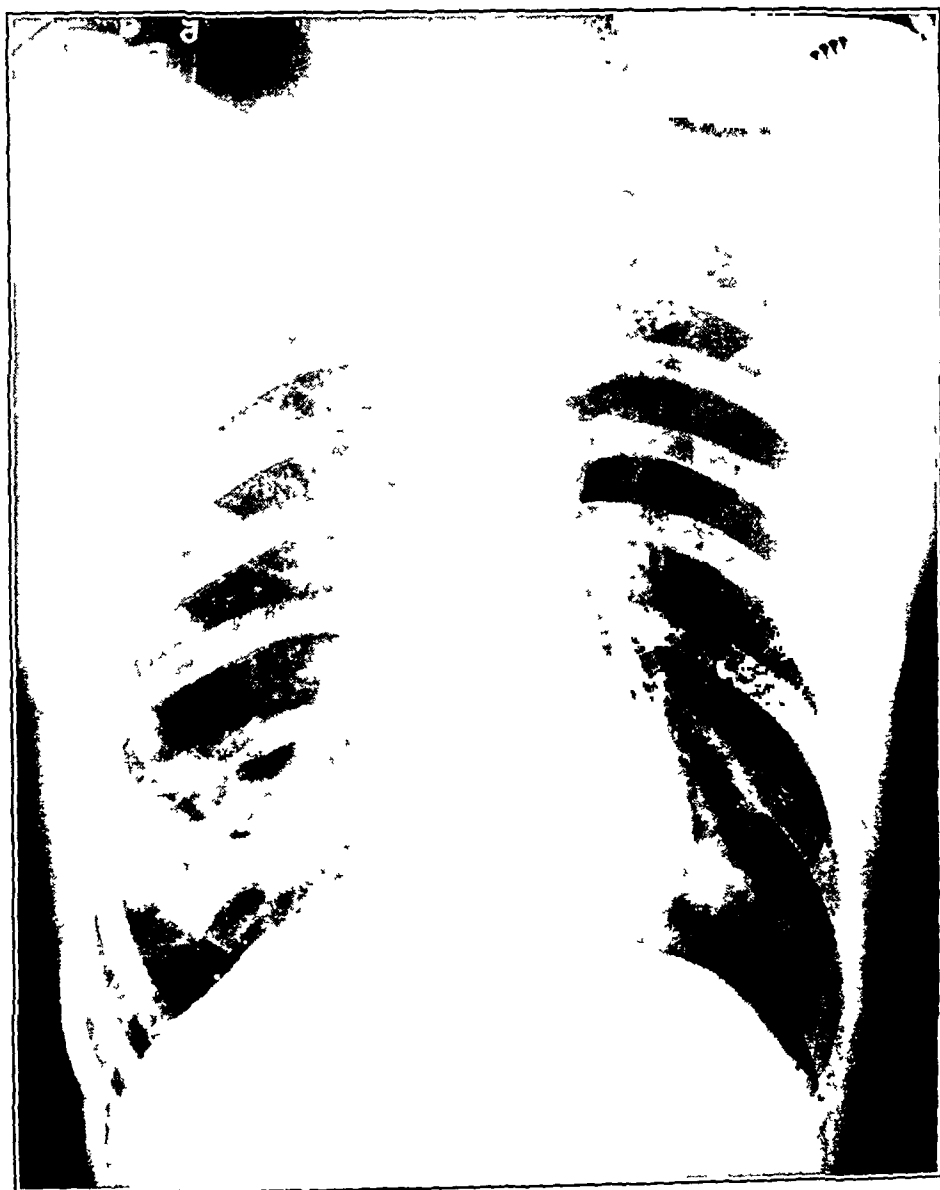


Fig. 1.—Roentgenogram of the thorax revealing what appears to be bronchiectasis in the lower right portion of the thorax. This represents the region in which two dilated vessels, originating in the right hilum, appeared to communicate in the parenchyma of the lung. An arteriovenous bruit was audible over this region.

had been administered daily. He remained there nine months. Thereafter, and until a month before his second visit to the clinic, he had taken 4 minims (0.25 c.c.) of solution of potassium arsenite (Fowler's solution) three times a day.

At the time of this second admission the patient appeared undernourished. Clubbing of the fingers and toes and cyanosis were about the same as before. The peripheral veins were dilated, especially those of the right anterior portion of the thorax and those of the legs; the latter were rather conspicuously varicose. A continuous, blowing murmur, or bruit, was heard over the right posterolateral aspect of the thorax, in the region of the eighth and ninth ribs. This murmur had not been heard when the patient was examined at the clinic in 1932, but he said that it had been heard by an army medical officer in 1916. The edge of the liver was palpable 5 cm. below the right costal margin. The blood pressure (94/60) was scarcely higher than it had been at the previous admission, and the temperature remained normal. The pulse rate, however, which had been slow in 1932, was 74. The retinal arteries and veins were dilated and appeared cyanotic, and the margins of the optic disks were slightly blurred. A number of punctate patches characteristic of old, chronic choroiditis were present.

The urine contained a few erythrocytes and pus cells. The value for hemoglobin was 23.7 gm. per 100 c.c. The erythrocytes numbered 6,470,000, the leucocytes, 7,300, and the platelets, 104,000. The hematocrit reading was 66 per cent on one day, and 71 per cent four days later. The total plasma volume was 1760 c.c., or 35 c.c. per kg. of body weight, and the whole blood volume was 6068 c.c., or 121 c.c. per kg. (normal, 85 c.c. per kg.). The electrocardiogram revealed a rate of 67, sinus bradycardia, slurred QRS complexes in Leads II and III, inverted T waves in Lead III, and positive T waves in the standard fourth lead. Roentgenoscopic examination gave evidence that the heart and mediastinum were normal, except for small patches of calcification in the anterior portion of the pericardium. There was infiltration of the posterior portion of the base of the right lung which was thought to be the result of bronchiectasis, as no pulsation was noted. However, the history did not suggest chronic bronchiectasis. Bronchoscopic examination, moreover, was deemed inadvisable.

An attempt was made to visualize a vascular lesion in the right side of the thorax. A radiopaque medium was injected into the basilic vein; then a series of roentgenograms was made. These revealed two dilated vessels arising in the right hilum, and communicating in the parenchyma of the right lung in the region of the ninth and tenth ribs posteriorly (Fig. 1). This region corresponded with that where the bruit was audible.

The probable diagnosis was now arteriovenous fistula of the right lung. Treatment consisted of venesection at frequent intervals, to keep the blood volume within normal range.

COMMENT

From an anatomic standpoint, the lesion in the right lung could properly be classified as an hemangioma, but physiologically it represented an arteriovenous fistula, and we felt that the increased blood volume was a result of such a fistula. That increase in blood volume is invariable in the presence of large arteriovenous fistulas is well known. Cardiac dilatation and hypertrophy also would be expected; their absence in this case perhaps was due to the fact that the arteriovenous fistula involved only the pulmonary circulation.

Hemangiomas usually are described as irregular, intercommunicating blood spaces surrounded by fibrillary connective tissue and smooth

muscle. They are divided into the simple, or capillary, nevus, the cavernous nevus, and the plexiform nevus. Hemangiomas vary greatly in size and shape; some are recognizable only with the aid of the microscope, while others weigh several pounds. Virchow long ago demonstrated that the intercommunicating blood spaces in hemangiomas really represent abnormal arteriovenous communications. In the so-called cavernous and plexiform types, bruits are often present. Many additional descriptive terms, such as "pulsating venous aneurysm," "angioma arteriole," and "arteriovenous varix," have been used to describe the superficial manifestations of a pathologic process which we prefer to call "arteriovenous fistula." Irrespective of size and shape, and notwithstanding the presence of a bruit, all hemangiomas represent abnormal arteriovenous communications between arteries and veins, by means of which arterial blood flows from arteries to veins without passing through the normal capillary bed. Reid¹ and one of us (Horton²) have held this view for a number of years.

Bowers,³ in 1936, reported the case of a child who died suddenly, on the second day after birth, from a fatal pulmonary hemorrhage. The source of the hemorrhage was found to be an hemangioma of the lung. Rodes⁴ also reported a case in which a man, 25 years of age, died suddenly from pulmonary hemorrhage; it was found that an hemangioma of the lung had ruptured. No mention of a bruit over the thorax was made in reports of these cases. The diagnosis in each instance was made at necropsy. We have no doubt that the condition in our case corresponded with that reported by Bowers and by Rodes.

REFERENCES

1. Reid, M. R.: Studies on Abnormal Arteriovenous Communications, Acquired and Congenital. I. Report of a Series of Cases, *Arch. Surg.* 10: 601, 1925. II. The Origin and Nature of Arteriovenous Aneurysms, Cirroid Aneurysms and Simple Angiomas, *ibid.* 10: 996, 1925. III. The Effects of Abnormal Arteriovenous Communications on the Heart, Blood Vessels and Other Structures, *ibid.* 11: 25, 1925. IV. The Treatment of Abnormal Arteriovenous Communications, *ibid.* 11: 237, 1925.
2. Horton, B. T.: Hemihypertrophy of Extremities Associated with Congenital Arteriovenous Fistula, *J. A. M. A.* 98: 373, 1932.
3. Bowers, W. F.: Rupture of Visceral Hemangioma as Cause of Death; With Report of a Case of Pulmonary Hemangioma, *Nebraska M. J.* 21: 55, 1936.
4. Rodes, C. B.: Cavernous Hemangiomas of the Lung with Secondary Polycythemia, *J. A. M. A.* 110: 1914, 1938.

Society Transactions

AMERICAN HEART ASSOCIATION, 1939

The opening session of the Fifteenth Scientific Meeting of the American Heart Association, held at the Jefferson Hotel, St. Louis, Mo., May 12 to 13, 1939, opened at nine-forty o'clock. Dr. William D. Stroud, Philadelphia, President of the Association, presiding.

President Stroud.—Members of the American Heart Association, friends, and guests: First of all, on behalf of the Officers and the Regional Board of Directors of the American Heart Association, I should like to welcome you to this, our Fifteenth Annual Meeting.

The papers this morning are open for frank discussion, but it has been deemed wise to limit the discussion to members of the Association and invited guests.

Unfortunately, it has been the custom for your president to make an address. I tried to escape this for your sake, but everyone seemed to think it had to be done. For the few remarks that I wish to make I have chosen the subject of "Fear in Medicine." I have been a little worried concerning this subject for many years, and feel that, as a public health organization, the American Heart Association assumes a grave responsibility with respect to the manner in which it presents to the public the subject of the prevention and relief of heart disease.

I think that everybody, naturally, is afraid of heart disease, and that there is grave danger that overemphasis of this subject, its fatality, its dangers, and so forth, may produce in this country of ours a great many introspective, apprehensive, psychotic individuals who are afraid of heart disease, but have nothing wrong with their cardiovascular system, any more than God expected them to have as they grow older.

I can remember some of the pamphlets that were distributed in 1923 or 1924 about "How Is Your Heart?" I remember one, especially, which said, "Your heart is a pump; take care of it," and showed a picture of a pump and a skeleton working at the handle. That sort of publication, I am afraid, isn't very valuable as a public health contribution. The English certainly feel that we are taking grave chances in bringing too much of this subject before the public, which is not well enough trained to really understand what it is all about.

First of all, in the last twenty years that I have been specializing in cardiovascular disease, I have seen more children and more adults—parents, that is—made cardiac cripples by the vague and serious prognostications of solicitous physicians than have been invalidated by rheumatic heart disease itself. I think we all admit that, as the years go by, we realize that probably seventy-five per cent of children with rheumatic heart disease do very well until their 30's, and some until their 40's or 50's. During the intervening years—except for the twenty-five per cent who have the disease in a recurrent or acute fulminating form, and die in childhood—these patients with rheumatic heart disease need not be made invalids until they reach their 30's or 40's, when their disease will incapacitate them anyway.

As for blood pressure, a recent patient of mine, seventy years old, a rather skeptical gentleman, remarked, as I reached for the blood pressure apparatus, "That is all a racket. According to the doctor, your blood pressure is never right.

Twenty years ago they started treating me for low blood pressure, and for the last ten years they have been treating me for high blood pressure. If they had only let me alone, I should be all right."

I believe there is something to this, except that I doubt if the treatment for low blood pressure had very much to do with his high blood pressure. As a matter of fact, most of us realize that we can do little about low blood pressure, unless there are some very obvious factors which are producing it. Usually, individuals with low blood pressure can be patted on the back and told that God has been very kind to them. They probably do not accomplish quite as much as the high-blooded individuals, but they are wonderful from the standpoint of the physician. They never feel quite right, they are always coming back to him, and they live forever.

With respect to coronary disease, it seems to me that since *Time*, *Fortune*, and our friends, the newspapers, are bringing this subject before the public, and most of the death notices give coronary occlusion as the cause of death, it is perfectly natural for people generally to link this condition with themselves, and feel that if their doctor tells them they have coronary disease, they are through.

I feel, personally, that it is very questionable whether a doctor—except in unusual cases—should ever tell a patient that he has coronary disease or angina pectoris, or that he has had a cardiac infarction. Sometimes it is necessary to do this to make a patient follow the proper regime.

This business has progressed to a point where—some of you have heard me tell of this experience—a few months ago a patient came in and said, "Doctor, my family physician says I have had a coroner's occlusion." It does seem to me it is a little startling to be told that one has had a "coroner's" occlusion. It makes one stop and think. I believe—as I have said before—that if these individuals ask you, "Do I have angina pectoris?" you are justified in saying, "No, you have temporary anoxemia of a portion of your myocardium." At least that impresses them a bit, and they usually accept it—even doctors will accept it. To an individual with a "coroner's" occlusion, you can say, "No, you have a relatively permanent anoxemia of a portion of your myocardium."

Then if you explain carefully that, as they are growing older, the stress, strain, and emotions of life place a burden on the circulation, and that, at times, if the blood pressure rises slightly above normal, because of emotion, or effort, or obesity, or indiscretions in diet, it may place a little more strain on the heart than it likes, but that if they will stay within their limitations they will have no trouble, and live out their full expectancy of life. Such an explanation will be of more benefit than telling them that they have angina pectoris, coronary disease, or coronary occlusion.

My thoughts are the same concerning unnecessary fears developed through electrocardiographic interpretations. I remember that the last thing Sir Thomas Lewis told me, in 1919, when I was working with him, was "When you return to the United States, you must be careful in using the electrocardiographic galvanometer. Remember that the United States is a young country, and Americans are impressionable. They believe that almost anything may be accomplished through mechanical or scientific effort. If you use this machine, then look at the tracing in front of the patient, and then look at the patient and shake your head, that patient is probably a cardiac cripple for the rest of his life."

I shall never forget when we first started taking tracings at the Pennsylvania Hospital, in 1920. I had to take them at night on the ward patients. We moved a colored patient in his bed to the heart station. You may remember the old galvanometer which reached all the way across the room. There were open batteries in the corner, and when in use it went "phfft," "phfft," and green lights flashed

in the darkness. I turned on the machine and the old colored fellow sat right up in bed. All I could see were his nightshirt and the whites of his eyes. He said, "Doctor, do you mind if I say a little prayer before you turn that thing on?"

Even those with more intelligence than this fellow have an awe of the galvanometer, and many of them come to you the week after the tracing has been taken and remark, "I felt ever so much better since I took that electrocardiographic treatment."

I believe that with all these machines now being sold throughout the country we must be sure to educate not only the public, but also the medical profession, as to the relative importance of the electrocardiogram. We must persuade doctor and patient, alike, that it is impossible to read from an electrocardiogram alone the last word as to the future of the cardiovascular system. I am positive that all too many physicians are attempting to read from electrocardiograms more than is justifiable.

In concluding these remarks, I should like to leave with you the thought that we must attempt to dispel some of the fear in the mind of the average person concerning cardiovascular disease. Certainly we have enough to be afraid of nowadays—social security, the administration in Washington, wars in Europe, many, many things. If we can give our patients a philosophy of life and hope and faith, I believe that we are helping them more than if we make them fearful.

General Cardiac Program

Discussion of the paper, "Possible Relationship Between Gall Bladder Disease and Cardiac Disease," by Dr. Henry L. Bockus, Dr. William D. Stroud, Dr. Paul H. Twaddle, Philadelphia, Pa., and Dr. Dolph L. Curb, Galveston, Texas.

Dr. Arlie R. Barnes, Rochester, Minn.—This is a subject that deserves a little discussion. I think Dr. Stroud is to be commended for the conservative and cautious attitude and conclusions which he has reached as a result of his studies thus far. There is some evidence to make us feel that disturbances of lipid metabolism are associated both with coronary disease and with disease of the biliary tract.

If Dr. Stroud had found that removal of an infected gall bladder resulted in reduction in the lipids, one would feel a little bit more encouraged to think that possibly such a procedure might be expected to improve disease of the coronary vessels.

Dr. Stroud very properly has emphasized the difficulties in differential diagnosis in these conditions. It is this difficulty that I think at times has given rise to the impression that the removal of the gall bladder has been a potent factor in improving the condition of the coronary arteries.

I have seen, for example, patients who had received a diagnosis of coronary disease and were put on a semi-invalid regimen for a period of three or four years. Subsequently, violent symptoms necessitated exploration of the gall bladder in each case, revealing stones and, at times, acute empyema of the gall bladder. Removal of the gall bladder in these patients dissipated the angina pectoris.

Such mistakes in diagnosis are likely to give an erroneous impression of the effect that removal of the gall bladder has on alleged heart disease.

This organization has a real responsibility in the opinion that it advances on this subject in relation to surgery. Surgeons are always looking for some new field in which to employ their art and to help us out. It is an honest attempt. If we give them reason to feel that the removal of an infected gall bladder or a diseased gall bladder gives very much promise of improving coronary disease, we are likely to see some operations performed that are not indicated. So, I am very glad that Dr. Stroud has been very cautious in his remarks, because, as far as my own personal experience is concerned, in relation to angina pectoris at least,

I have not been impressed with the fact that the removal of an infected gall bladder or a gall bladder with stones has influenced the degree or progress of coronary sclerosis.

Dr. Myron Prinzmetal, Los Angeles, Calif.—At the Boston City Hospital, Dr. Soma Weiss and I made electrocardiographic tracings routinely on patients with gall bladder colic, either with or without jaundice, but with very severe pain. We were surprised to find occasional cases in which there were definite electrocardiographic changes when pain was present, which disappeared after the gall bladder colic was over. This suggests that there may be a reflex from the gall bladder which may produce cardiac changes of some type or other, such as have been observed by Dr. Stroud.

Dr. Walter B. Hamburger, Chicago, Ill.—This subject, as Dr. Stroud well knows, is a very old one. I believe that it was about 1854 when Stokes first called attention to it.

In Chicago, Dr. Robert Babcock was the first, so far as I know, to emphasize this relationship, and for many years had many of his cardiac patients operated on. On what basis Dr. Babcock reasoned this out I don't think anyone knows.

Following his time, Frank Billings did the same thing, on the assumption, I believe, that the gall bladder served as a focus of infection, and, certainly, during the time I was with him, I saw quite a few cardiac cases in which Dr. Billings advised surgical operations on the gall bladder.

About fifteen years ago Dr. D. C. Straus and I were interested in a group of patients with extrasystoles and gall bladder disease. Several of these patients were operated on. Interestingly enough, most of their extrasystoles disappeared. As Dr. Stroud said, they may have been cured by removal of the gall bladder, or by the anesthetic, or by some other mechanism. However, in my own experience, extrasystoles and other cardiac arrhythmias do seem to have a relationship to the gall bladder.

I have under my care at the present time a woman with recurring attacks of severe auricular paroxysmal tachycardia. She has a number of gallstones which she will not permit us to remove. However, with indiscretions of diet, her attacks are very much more frequent. When she is quite careful of her diet, her attacks are relieved.

I feel that Dr. Stroud and his associates have done a fine thing in again subjecting this question to careful study. So far as I know the study of a large series such as theirs has never been made, and as a result we should find out exactly what, if any, this relationship is.

Dr. Charles N. Hensel, St. Paul, Minn.—I was very much interested in Dr. Stroud's report of the case of the woman who had experienced repeated attacks of pain (which at one time were thought by an Italian heart specialist to be due to coronary disease), who died in this country, and was found at autopsy to have relatively normal coronary arteries and disease of the gall bladder.

I can match his case with one of my own, in which, at autopsy, the findings were reversed. My case was that of a woman, a nurse, married at the age of 44 years, who had a stormy married life. I saw her first six years before her death, in a paroxysm of auricular fibrillation; at this time the electrocardiogram revealed evidence of a previous coronary occlusion. Ever thereafter she had paroxysms of auricular fibrillation, frequently associated with emotional stress, but no epigastric distress or precordial pain.

The final episode was ushered in by a state of extreme emotionalism and the complaint of a severe burning sensation in the epigastrium. The heart was normal with respect to sounds, rate, and rhythm. Her blood pressure was at the usual level of 150/80.

The abdomen was soft, and there was no tenderness over the gall bladder or in the epigastrium. Sedatives and antispasmodics were prescribed, and three days later the patient had improved sufficiently to go through with a previously planned dinner party.

She spent a sleepless night, and the next morning was seen at home, sitting up in bed, rocking back and forth, apparently in great distress, still complaining of a terrific burning sensation in the epigastrium. The heart was unchanged and the lungs were clear, but now for the first time there were definite tenderness and muscle spasm over the gall bladder. Cholecystograms showed nothing abnormal, but the patient continued to complain of burning pain in the epigastrium. Symptoms of cardiac failure eventually appeared, and the patient died three weeks after the first complaint of burning in the epigastrium.

At autopsy the gall bladder was normal, but the heart showed evidences of an old infarction in the left ventricle, plus a fresh occlusion throughout the main descending branch of the right coronary artery. Microscopically, the lesions in the freshly infarcted area were from a few days to three weeks old.

In this case then, the symptoms were suggestive of gall bladder disease, but the autopsy showed that coronary occlusion was the true cause.

Dr. Louis N. Katz, Chicago, Ill.—It is difficult to determine whether gall bladder disease perpetuates or aggravates coronary disease, but there is no doubt that reflexes come from the gall bladder which affect the heart, as was shown by Drs. Bettman and Rubinfeld at Michael Reese Hospital. In the presence of gall bladder disease such reflexes may, when coronary disease is already present, aggravate the symptoms of both the gall bladder and the heart condition.

It seems to me possible that such reflexes may actually lead to coronary spasm. While I agree with Dr. Barnes that the surgeon should not be encouraged to operate on gall bladders to relieve heart symptoms, I have occasionally seen some good results from such gall bladder operations. Pain is a sensation, and painful stimuli that may be below the threshold in the heart may summate with painful stimuli from the gall bladder, and the two together reach the field of consciousness of the patient. Little can be done operatively for the heart in such cases, but removal of the irritation in the gall bladder may make the patient more comfortable by eliminating one source of the bombardment of impulses that gives rise to pain.

Dr. Carl R. Comstock, Saratoga, N. Y.—I do not wish to prolong this discussion unduly, but very recently a patient at Saratoga (by the way, a surgeon) who had had coronary attacks for many years and also, apparently, gall bladder attacks, was operated upon.

His electrocardiogram showed no material change except left axis deviation. Cholecystograms showed numerous stones in the gall bladder. The gall bladder attacks, usually coming on at night, were quite severe, and would precipitate an anginal attack, with pain down the left arm.

He was operated on two months ago, has had no further attack, and is apparently perfectly well. His electrocardiograms are the same as before. There does seem to be some interrelationship in the distribution of gall bladder and coronary pain.

Discussion of the paper, "Factors in the Circulatory Changes Associated With Pregnancy," by Dr. J. Allen Kennedy, and Dr. C. Sidney Burwell, Boston, Mass.

Dr. Burwell.—I would like to say a word, if I may, Dr. Stroud. I want to emphasize the fact that pregnancy is a particularly suitable condition for the study of dynamics of the circulation, because every patient studied establishes her own control. She can be studied after delivery, and the results under these circumstances can be compared with the results during pregnancy.

I also think it is only proper to express to these admirable subjects who have subjected themselves to our study a vote of thanks, on the part of Dr. Kennedy and my other colleagues and myself, because they really did very good work, and they were extremely cooperative in establishing basal conditions. It is necessary, of course, to have very carefully controlled basal conditions if these observations are to be significant.

The observations that Dr. Kennedy has presented are, of course, a small part of many that have been made by many workers in the last ten years on the circulatory changes in pregnancy. Out of all of these observations, it seems that there is coming a reasonably coherent description of the total changes in the circulation in pregnancy which will enable us to guide patients with heart disease through this trying period.

I am talking now only about the burden of pregnancy itself. There is nothing in this work that bears on the burden of *labor*. But if one interprets the changes in the course of heart disease, which are brought about by pregnancy, in terms of the increased cardiac work imposed by the pregnancy, one gets a pretty reasonable explanation of the events which one sees.

One of the interesting observations that has been made by Burton Hamilton is that the incidence of the onset of cardiac failure corresponds in a large series of cases quite reasonably accurately with the calculated curve of the increased work of the heart.

Therefore, it seems to me that these observations of Kennedy and his colleagues have a very definite application to the care of patients with heart disease and pregnancy. The object of our efforts in the care of heart disease in pregnancy is mainly to protect the patient against removable burdens. The burden of pregnancy is inescapable. It is a necessary part of the body's reaction to pregnancy. The function of a physician then becomes that of helping the pregnant woman avoid other forms of cardiac overwork.

Discussion of the paper, "Cardiac Changes in Pregnancy Unrelated to the Usual Etiologic Types of Heart Disease," by Dr. William A. Sodeman, New Orleans, La.

Dr. C. Sidney Burwell, Boston, Mass.—Dr. Sodeman's very instructive paper offers many pleasant points for discussion. I hope that in the informality of the discussion period he will say what he thinks about the mechanism of these very interesting basal diastolic murmurs that appear during pregnancy and disappear during the puerperal period. I think that is a very attractive question to ask.

Now, he has emphasized how incomplete a description of the circulatory changes in pregnancy is really put on record by the observations just mentioned by Dr. Kennedy, because there are, as a matter of fact, three or four major groups of alterations in the circulation during pregnancy. One includes those that Kennedy described, that are concerned mainly with changes in the uterus and the placenta and with the immediate demands of the fetus. There are also those that nobody has mentioned yet, those of labor itself. Dr. Sodeman now points out there are also those of the puerperal period. He emphasizes that cardiac failure may appear during that period. I do not know anything about the circulatory burdens that occur during the puerperium, but I should like to ask Dr. Sodeman to comment, and to present evidence, if he has it, about the developments during lactation that produce changes in the circulation. Certainly the circulation of the breast is enormous during this period, and, also, the sudden production and excretion of a large amount of nutritive fluid must take away from the maternal body a considerable amount of accessory nutritional substances, such as vitamin B₁₂, for example. It is just possible that that plays a role, and I would like to ask him that question.

Finally I should like to make, in connection with his very interesting description of the occurrence of heart failure in people with hypertensive disease during pregnancy, one point of warning concerning the management of these people. It applies to a large group of cardiacs, not only to the pregnant woman. I am sure that it is familiar to you all, but it is worth emphasizing.

One of the effects of pregnancy is to increase the blood volume. One of the effects of the development of congestive heart failure is to increase the blood volume. By injecting large amounts of fluid into perfectly normal animals rapidly enough, a picture can be produced which is certainly very similar to that of cardiac failure.

Many of us have seen a considerable number of attacks of paroxysmal pulmonary edema, threatening life, follow, by a short interval, the injection, in considerable amounts, of fluid intravenously.

Now, in certain stages of hypertensive toxemic disease in pregnant women, it may be useful to inject fluid intravenously. I simply remind you that the injection of 500 c.c., or 1,000 c.c., or 1,500 c.c., of fluid into the veins of a woman who already has a large blood volume from pregnancy and increasing blood volume from advancing heart failure may very well be the final factor that precipitates the onset of serious and even dangerous cardiac failure.

Dr. Sodeman.—I know nothing about the development of these basal murmurs, Dr. Burwell. I do not think they occur as frequently as once in seventy-three patients. It probably just happened that this rare finding did occur in this group of seventy-three patients, and, if we examined 1,000 more pregnant women, perhaps we would not find one; perhaps we would find more; I don't know. The murmur disappeared in the post-partum period, and the patient has been followed for a number of years since. Nothing happened, as far as cardiac changes were concerned.

These patients with post-partum heart failure were all colored patients. They were all seen on the wards of Charity Hospital, in New Orleans. Just exactly what causes this picture, what is most important in its etiology, I do not know. Most of these patients do have some form of dietary deficiency which may have a bearing on the etiology.

As to the effects of lactation on the heart in the puerperal period, I know only one thing, and that is that the blood pressure often rises somewhat, not to abnormal levels, however, with the onset of lactation. Whether there are any other changes or not, and whether there are any other changes of importance, I cannot say.

Dr. Julius Jensen, St. Louis, Mo.—Because there is so much to be said about these last two papers, it is impossible to discuss them in detail. I would only like to point out two observations.

The first one is regarding circulatory changes during pregnancy. We, of course, are all impressed by the tremendous amount of work which has been done by Dr. Burwell and his co-workers, and we are gratified that, on the whole, their findings confirm earlier, but less securely founded, views.

Only on one point would I beg to disagree: It seems to me that the general impression is that during pregnancy the blood pressure has a tendency to rise, remaining, however, within normal limits. This applies both to the systolic and the diastolic pressures.

Whenever we are considering changes during pregnancy, I think we should draw a definite distinction between those changes which are generally acceptable for all persons and those that vary according to certain constitutional factors in the individual. Therefore, I think we should be careful not to draw too general conclusions from our observations. If we may assume that certain pathologic changes of pregnancy are merely exaggerations of physiologic changes, I can illustrate what I mean with the following observations: Hypertension is either not affected or is aggravated by pregnancy. In rare cases, however, we find an elevated blood pressure

returning to a normal level during pregnancy. It is difficult to understand how a mechanism common to all women with hypertension could have such divergent effects.

I would also like to say just a few words about functional heart disease. In general, authors and observers seem to take rather a lenient view of this so-called "functional" disorder. However, Dr. Sodeman has just intimated that there may be changes in the myocardium during pregnancy with which we are as yet but vaguely familiar, and other observations seem to point the same way.

It seems to me that we must, at least for the present, take a very cautious view as to the possible significance of any cardiac symptoms which occur during pregnancy.

Discussion of the paper, "A Study of Marked Coronary Arteriosclerosis in Patients With and Without Angina Pectoris and Related Conditions," by Dr. H. L. Blumgart, Dr. Monroe J. Schlesinger, and Dr. David Davis, Boston, Mass.

Dr. Charles N. Hensel, St. Paul, Minn.—I would like to ask Dr. Blumgart if he would care to comment, with regard to these cases of multiple occlusion of the coronary arteries, on the relationship of the Thebesian canal, and I would also like to ask him whether, with so many infarctions, the hearts are large or heavy.

Dr. H. L. Blumgart, Boston, Mass.—The heart weights of the patients with angina pectoris and multiple occlusions varied widely, from 280 to 610 grams.

The first diagram which I showed was that of a 510-gram heart, and the second was of a 350-gram heart. In the first case arterial hypertension had been present. In the second case it had not been present. In brief, then, these hearts are, of course, somewhat above normal weight, but they are not enormous hearts.

Dr. Hensel.—What about the Thebesian canal?

Dr. Blumgart.—That awaits further study. All I can say is that the material is injected into the right and left coronary arteries, and there is no evidence in our work as to the importance of the Thebesian channels or backflow from ventricular cavities.

Dr. Daniel J. Glomset, Des Moines, Iowa.—I should like to discuss Dr. Blumgart's paper in relation to the influence of anastomosis in the coronary circulation. In addition to the anastomosis which he has so beautifully illustrated, there are two other important ways in which the myocardium is supplied with blood.

First, there are frequently one or more accessory coronary arteries. Thus, a patient of mine was kept alive by a large descending right artery after his left anterior descending branch and circumflex artery had been occluded.

The second important accessory circulation comes from the pericardial and endocardial surfaces. The value of this was shown in another case of mine, in which the left coronary was occluded at its mouth. Yet the individual lived for twelve days. Necropsy revealed a vascular pericarditis. The infarct which was present involved the entire left ventricle, but the myocardium was necrotic only in the middle. The pericardial and the endocardial thirds of the myocardium were normal.

Discussion of the papers, "A Study of Marked Coronary Arteriosclerosis in Patients With and Without Angina Pectoris and Related Conditions," by Dr. H. L. Blumgart, Dr. Monroe Schlesinger, and Dr. David Davis, Boston, Mass., and "Coronary Artery Occlusion: Clinical and Pathological Correlation (Analysis of 144 Fatal Cases)," by Dr. A. M. Master, Dr. Henry Horn, Dr. Simon Dack, Dr. Harry L. Jaffe, and Dr. Leonard Finklestein, New York, N. Y.

Dr. M. A. Kugel, Miami Beach, Fla.—I must apologize for speaking at this late hour. In the eleven years of my association with the late Dr. Louis Gross, we devoted much time to the study of coronary circulation.

When we first started our studies, which are similar to those described today by Dr. Blumgart, we were impressed with the fact that the usual technical methods did not give us an accurate or complete picture of the coronary artery circulation. The hearts which we injected with barium sulphate gelatin were roentgenographed and then cleared by the method of Spalteholz. Then, by means of dissection of the cleared specimens, we were able to demonstrate anastomoses between coronary arteries which could not have been artifacts caused by technical methods.

In this way we discovered the arteria anastomica magna, which is located in the intra-auricular septum, and provides a collateral circulation between the main left and right coronary arteries, as well as with the artery supplying the A-V. node. A detailed description of this hitherto undescribed anastomotic vessel was published by me in the *American Heart Journal* in 1928. The vessel appears to be functionally important, particularly in cases of occlusion of the right coronary artery, in which one may find transient electrocardiographic changes referable to disturbances in the function of the A-V node. These transient electrocardiographic changes have been attributed by others to the anatomic location and the potential functional capacity of the anastomotic artery in establishing collateral circulation to the A-V node. An occlusion of the right coronary artery temporarily interrupts the circulation to the A-V node, which is normally supplied by a branch of this artery.

In general, we found that the collateral anastomotic channels enlarge in the late years of life, or there has been a partial or complete occlusion of the coronary arteries.

Finally, Dr. Blumgart brought out the important observation that one not infrequently finds hearts with multiple occlusions in the coronary arteries. The survival after many occlusions may also be dependent upon the state of the coronary artery circulation, the anastomoses, and even anomalous coronary arteries. We reported a case a few years ago of a man who had three coronary arteries; the left circumflex coronary artery had an independent origin. The right and left coronary arteries were both completely occluded at several points, and the circulation to the heart was apparently carried on by the accessory coronary artery through its anastomoses.

We refused to draw too many conclusions from purely anatomic observations, but in many of the hearts the damage was so extensive that one often wondered at the remarkable ability of the heart to maintain its circulation. The more we studied the coronary artery circulation, the less able we were to arrive at specific conclusions, but we were impressed with the fact that the heart under duress has a tremendous power of changing the course of its circulation for the better.

Dr. Blumgart.—I am very glad that the previous discussor mentioned the work of Dr. Gross and his associates, to whom we are all indebted for their splendid contributions in this field. Every investigator always hopes that there will be advances beyond what he has been able to accomplish. I think Dr. Schlesinger's method of unrolling the heart in one plane, using multicolored injection masses, and avoiding confusion by overlying vessels, is a significant contribution.

I do not want to be misinterpreted to the effect that what has been portrayed in these cases will be an invariable finding, because, after all, we have had but twelve cases of angina pectoris in this series and are still continuing our studies. Each case is a study in itself.

I was interested in hearing from the first discussor about his experience in finding collateral circulation developed through an adherent pericardium. This illustrates my previous remark, because in three cases in which we found old infarcts and an adherent pericardium no injection mass passed from the coronary circulation

through any vessels to that adherent area, as would have been expected in view of the very interesting work of Dr. Beck and his associates.

We find, likewise, that the right coronary artery is more frequently involved than any other. One not infrequently observes "infarctions at a distance," that is, infarctions of the left ventricle from occlusions of the right coronary artery. After occlusion, for instance, of the left anterior descending artery, the peripheral portion of that artery and the myocardium which it normally supplies will be vascularized by collateral circulation emanating from the right coronary artery. When the right coronary artery is then suddenly occluded, the anastomotic circulation to the left ventricle is no longer effective, and infarct occurs, for example, in the apex of the left ventricle, when the occlusion may be near the mouth of the right coronary.

It is important, in making post-mortem dissections, not to have one's mind come to rest when one fails to find an arterial occlusion in relation to the area which is infarcted.

Dr. A. R. Barnes, Rochester, Minn.—I should like to make one or two remarks in connection with what Dr. Blumgart has said, which corroborate an impression he has just given.

Dr. Burchell, working in our laboratories, has undertaken to reinvestigate the question of establishing collateral circulation by producing adhesions to the heart, either through muscle or omental grafts.

In the process of this investigation, after having attached either muscle or omental grafts to the myocardium, the coronary circulation was interrupted by stages until all three branches were finally occluded, and the animal was allowed to live.

Strangely enough, he found exactly what Dr. Blumgart found, that if these vessels are occluded one at a time, the remaining branches establish a collateral circulation of their own which is sufficient to maintain the heart in excellent function, and that function is derived from these anastomoses and not from anastomoses that are the result of the attachment of muscle or omentum to the heart.

Injection either from the heart side or from the side of omental or muscle graft did not show any appreciable amount of circulation going through these omental or muscle grafts.

Moreover, after all three branches, or branches of three main vessels, had been interrupted, the dog was able to carry out a normal amount of work on the treadmill because of this sufficient collateral circulation. If he now interrupted the grafts by cutting them off, there was no loss of the dog's ability to carry out exercises.

Dr. Arthur M. Master, New York, N. Y.—I was interested in the case that Dr. Blumgart described in which there were nine old occlusions. Our pathologists, particularly Dr. Horn, find it difficult to make a diagnosis of old occlusions. I know they do occur, and it may be that Dr. Blumgart's method is an improvement on routine pathologic procedures. We have all had patients with many occlusions. I have had two patients with five closures, typical clinically and electrocardiographically, and they are both alive at the present moment.

I was interested to hear Dr. Blumgart talk about postoperative shock as a cause of coronary occlusion. We have noted that coronary occlusion does occur following an operation.

Mention was also made of the fact that, if a patient has severe coronary sclerosis and angina pectoris, rest is extremely important. I want to emphasize, however, that nobody has shown that effort will produce another occlusion, although I am sure it may cause death by coronary insufficiency. I also want to emphasize that term "coronary insufficiency," because I think that that is entirely different from

coronary artery occlusion. That is why I would prefer to use the term "coronary artery occlusion with cardiac infarction," than merely say "myocardial or cardiac infarction."

Discussion of the paper, "Production of Pressor Substance by Totally Ischemic Kidney," by Dr. Alberto C. Taquini, Buenos Aires, Argentina.

Dr. Louis N. Katz, Chicago, Ill.—The results which Dr. Taquini has presented on the direct demonstration of a pressor substance have not been confirmed entirely by others. Many investigators, including my associates and I, have failed to find any evidence of a pressor substance in the blood coming from an ischemic kidney.

In our work, we perfused unanesthetized, bilaterally nephrectomized dogs with the blood from dogs made hypertensive by the Goldblatt technique. Over a period of twenty-four or more hours, we replaced the blood of the nephrectomized non-hypertensive animal with the hypertensive blood two or three times, without any demonstrable elevation of blood pressure. When we perfused the hind limb of anesthetized dogs with the blood of anesthetized, hypertensive animals, the only effect obtained was dilatation, not constriction.

We all realize that everything points to a pressor substance, but I wonder whether the results of Taquini are not due to the liberation of renin by the severe ischemia, a sort of extraction in life?

Dr. Taquini (closing).—We have tried to produce muscle constriction with blood from the general circulation without success, but with blood taken directly from the kidney we obtained a wonderful muscle-constricting action. It seems that the blood from the totally ischemic kidney contains more of the pressor substance than that from the partially ischemic kidney, because when I tried to produce hypertension in the dog by direct injection of the blood from the ischemic kidney by another method, I failed. But with the blood from the previously ischemic kidney, I obtained results in all of the cases.

I have the results here, and I will read some of them. This is the rate of perfusion in the preparation of Löwen Trendelenburg.

In the first experiment, the number of dogs injected with Ringer's solution was 60; with plasma from the renal vein of a normal kidney, 66; with plasma from the totally ischemic kidney, 14. That means a diminution of about 65 per cent.

In the second experiment, the number of dogs injected with Ringer's was 71; with plasma from the renal vein of a normal kidney, 75; with plasma from the totally ischemic kidney, 2; making a diminution of about 95 per cent.

In the third experiment the number of dogs injected with Ringer's was 56; with plasma from the renal vein of a normal kidney, 63; with plasma from the totally ischemic kidney, 7, and so on. All of the experiments gave the same results.

We don't think that there may be changes in the secretory function, because, in the experience of Graffman and Kinney, only blood from the previously ischemic kidney produced, in the same dog, a marked pressor effect. The injection of 100 c.c. of blood from the normal kidney does not produce any change in the blood pressure of the animal, but with blood from a kidney previously made ischemic there was a great hypertension.

Discussion of the paper, "Clinical and Experimental Studies on Quinidine: With Clinical Application as to Method of Treatment in Auricular Fibrillation," by Dr. Samuel A. Weisman, Minneapolis, Minn.

Dr. Lewis A. Conner, New York City.—It seems to me that many of the points that Dr. Weisman has emphasized are fully deserving of such emphasis.

I have thought that we had all been convinced by this time that quinidine was not dangerous, in the ordinary sense of that word; and, if used wisely, was a valuable and relatively safe drug.

I am not sure that the method of giving quinidine in several doses close together during a part of the day, with nothing after that until the next day, is *theoretically* a satisfactory way.

Sir Thomas Lewis, as you know, back in 1925, I think, showed that, in order to restore the normal rhythm, certain changes in the circus movement had to be produced by the quinidine and maintained for a certain time. As I recall it, he showed that the effect of a single dose of quinidine was not longer than four, or five, or six hours. The inference was that one ought to maintain the quinidine effect by doses throughout the twenty-four hours, rather than having a long free interval at night.

Certainly, as I have used it, we have always continued the quinidine throughout the 24 hours. If we were using it in fairly large doses and expecting to get results within a very few days, two or three days, perhaps, we have always given it continuously through the night at four-hour intervals. Whether that is necessary or even desirable, I don't know.

There can be no doubt of the desirability of restoring the normal sinus rhythm in a great many cases, probably in most cases, of auricular fibrillation, but I should like to raise the question whether that applies to every case of auricular fibrillation. Of course, the ones that are most doubtful are those of advanced mitral stenosis. My feeling is that they are better off, often, without normal rhythm.

In the first place, the normal rhythm isn't likely to be maintained very long. There may be exceptions; doubtless there are exceptions to that rule, but a patient with high-grade mitral stenosis and auricular fibrillation does not very often, I think, maintain a normal rhythm once the quinidine has been given and has been effective.

But even if it does restore and maintain the sinus rhythm, I still raise the question whether that is a desirable thing in these advanced cases of mitral stenosis.

I don't know of any type of patient that is harder to treat effectively than just such a one with mitral stenosis who has *not* developed auricular fibrillation. The effects of digitalis are far less striking and satisfactory than when fibrillation is present.

If, with fibrillation, one can maintain the rate at 60 or 65, the patient usually is much better off than if he has sinus rhythm with a heart rate of 80, 90, or 100.

Dr. H. L. Smith, Rochester, Minn.—In treating any patient who has auricular fibrillation, it must be remembered that we all have seen a great number of patients with chronic auricular fibrillation that has continued for many years, yet these patients have been able to live and be reasonably active in spite of this fact.

I quite agree with the speaker that the occurrence of emboli as a result of administering quinidine has been greatly overemphasized.

I believe that there are certain patients to whom it is advisable to administer quinidine, such as, first, patients who have the so-called idiopathic auricular fibrillation, or patients who have fibrillation without any other evidence of organic heart disease; second, patients who have a minimal amount of heart disease and do not have fibrillation of long duration; and third, patients suffering from hyperthyroidism who continue to have fibrillation after thyroidectomy.

I question the advisability of attempting to establish normal rhythm in patients who have serious organic heart disease, and especially in those who have hypertensive and arteriosclerotic heart disease with marked hypertrophy.

I believe the greatest danger to such patients, if quinidine is administered to them, is that of sudden death. Sudden death in such instances is probably the result of depression of both the sinoauricular and auriculoventricular nodes for a

sufficient period to produce death. This danger must be considered seriously and weighed against the benefit that the patient receives when normal cardiac rhythm is re-established.

Dr. Thomas Lee, Washington, D. C.—I rise chiefly to ask Dr. Weisman if he would explain to us how it is that patients with auricular fibrillation whose heart rates may be reduced, as I believe they can in nearly all cases, to a reasonable figure, 60, 70 or 80, if you wish, lose as much as 75 per cent of their cardiac efficiency because of their fibrillation. The heart muscle is the same. One must revert, then, to the question of the advantage that is gained by having the auricles add their propulsive force to the circulation. Although it is very easy to conceive that it may be 15 per cent, and doubtless is sometimes more, I cannot quite see how the difference would rise to 75 per cent in the same heart.

I would feel with Dr. Weisman and the other speakers that it is very advantageous in most cases to have normal rhythm instead of auricular fibrillation. However, it cannot always be done.

I would like to bring forward the point that many patients can go on continuously with auricular fibrillation with very good function for a long period of time. As a matter of fact, I am reporting tomorrow, at a meeting of one of the other societies, a case in which fibrillation has been present for thirty-five years, which is, I believe, the longest duration that has been reported in medical literature; the patient, now nearing 70 years of age, has been very active all of that time. His ventricular rate has been kept between 70 and 80, and his functional capacity has been very good.

I don't wish to imply that I do not use quinidine very frequently. I think it is most effective in many cases. I think that in the type of case Dr. Smith has referred to, that is, in younger patients without very serious organic heart disease, it is most desirable to use it. But I want to emphasize the fact that in those cases in which its use is undesirable, especially including those which Dr. Conner has just spoken of, and those in which it is not effective, the heart may perform its function very satisfactorily, as has been brought out more and more in recent communications, for a long period, in spite of auricular fibrillation.

Dr. Joseph B. Wolfe, Philadelphia, Pa.—Many studies have already been made and reported on the use of quinidine in auricular fibrillation. A number of years ago we divided our cases of auricular fibrillation at the cardiac clinics of Temple University and Mt. Sinai Hospitals and treated some of the patients with maintenance doses of digitalis, while to others we gave quinidine in a manner similar to that which has been so well described by Dr. Weisman. Strange to say, we had very fine electrocardiograms to show as a result of the quinidine therapy. We restored normal rhythm in a great many cases, but we were amazed that over a period of time the mortality was greater in that group than among those who had been taking only maintenance doses of digitalis and, occasionally, quinidine, but without any idea of restoring normal rhythm. Particularly was that true of patients who suffered from arrested rheumatic heart disease with mitral stenosis.

We feel, therefore, that it is extremely important to consider the etiologic factor, rather than the disturbed physiologic state, before using quinidine.

No one doubts that quinidine is a most valuable drug. In cases of auricular fibrillation caused by thyrotoxicosis, in which the underlying cause has been eliminated, or in cases of paroxysmal auricular fibrillation either of unknown origin or caused by an autonomic disturbance, quinidine will aid in restoring the normal sinus rhythm, which greatly benefits the patient. On the other hand, in mitral stenosis we found it best to use it only as an adjunct, if necessary, together with digitalis, but by no means to attempt to restore normal rhythm. As a matter of

fact, we feel that auricular fibrillation is a protective mechanism in many cases of mitral stenosis, like soldiers breaking step while crossing a weak bridge.

If the pulse deficit and the heart rate are controlled, patients with auricular fibrillation may lead fairly long and useful lives. Strange as it may seem, very often at the bedside of a patient with advanced mitral stenosis who failed to respond to the ordinary methods of therapy, I have wished that we had some drug to induce auricular fibrillation.

Dr. Weisman (closing).—The greatest danger of embolus formation occurs in auricular fibrillation, more so, perhaps, than after normal rhythm has been restored.

Sir Thomas Lewis' experimental studies of the effect of quinidine on dogs showed that the maximum effect of the drug on the heart took place in about two hours. It was about twelve hours before the effect of quinidine was entirely gone, and almost twenty-four hours before the heart rate returned to normal. So, quinidine does have a prolonged action, but we do not know yet whether it is best to give the quinidine every hour or every two hours. So far, our work indicates that giving it every hour is very satisfactory.

In cases of mitral stenosis it is most difficult to restore to normal rhythm, but once normal rhythm returns, the patients seem to get along satisfactorily.

Dr. Smith: Many reports in the literature warn us against giving quinidine to old people, to patients with coronary disease, and to patients with mitral stenosis of long standing. Korns, of Cleveland, now of Iowa City, some years ago, in reporting his studies on quinidine, showed that some of the best results were obtained in old people, those with coronary disease, and patients who were more or less cardiac invalids. We, too, found that the most spectacular results were obtained in old people and in those with coronary disease and beginning signs of cardiac decompensation.

Dr. Lee brought up the question of the efficiency of the heart after normal rhythm had been restored. This has been studied time and time again by many investigators, among whom were Eyster and Swarthout, Smith, Walker, Alt, and, more recently, Kerkhof, of Minneapolis. Eyster and Swarthout showed that the efficiency of the heart diminished from 20 to 70 per cent when auricular fibrillation was present.

Dr. Kerkhof made a study of the cardiac output of a group of patients with mitral stenosis and auricular fibrillation before and after normal rhythm was restored. He found that there was an average increase of about 25 per cent in the cardiac output after normal rhythm was re-established.

Discussion of the paper, "Importance of Restriction of Salt as Compared to Water in Cardiac Failure," by Dr. Henry A. Schroeder, New York, N. Y.

Dr. Walter B. Hamburger, Chicago, Ill.—In reference to these very interesting observations on the restriction of salt in cardiac failure, I should like to ask Dr. Schroeder whether he believes the sodium or the chloride ion is the effective agent.

In his reply I would be interested to know what potassium chloride, as a substitute for sodium chloride, might do and also what role ammonium chloride, which is given with the mercurial diuretics, may play.

Dr. Schroeder (closing).—We have made no observations on the relative effect of sodium and chloride ions. It is known, however, that the sodium ion is important in edema due to low plasma proteins. The edema of congestive heart failure, although of different etiology, may be of similar mechanism, that is, a filtration edema. It is possible that the same factors with regard to the sodium ion are at work in both types of edema. No attempt has been made to evaluate the effects of the potassium and the ammonium ion.

Discussion of the paper, "The Clinical Use of the Lag-Screen Electrocardiogram,"
by Dr. Graham Asher, Kansas City, Mo.

Dr. Howard B. Sprague, Boston, Mass.—I should like to attest the excellence of this instrument that Dr. Asher has devised. I had the opportunity of seeing and using his model just before it was decided to put it into commercial production, and to act as a consultant on technical matters in the manufacture of the machine.

I think he has mentioned to you only the early immediate possibilities of the use of this instrument. Its usefulness is similar to that of the fluoroscope, as compared with the teleoroentgenogram. One of the other possibilities that could be mentioned is the routine checkup examinations of patients in offices, when one has a series of electrocardiograms on the same patient and does not feel that it is necessary to fill up the files with a lot of routine electrocardiograms. Another is the possibility of rapidly examining large groups of people, such as students, men for the army, insurance applicants, or the like.

It is now possible to stop the machine temporarily (it gives a very clear tracing), and to superimpose both time and amplitude lines for a short period on any part of the tracing that you wish. This is done by illumination through the back of the screen.

The two criticisms that I have heard about this instrument are that anyone who can interpret electrocardiograms, and, as Dr. Asher says, only such a person should use the machine, can get a pretty good idea of what is going on by watching the string shadow in the modern, portable instrument. But this instrument is far better.

The other criticism is one that I just recently heard. It was said that this machine made it so easy for the consultant to make the diagnosis at the bedside that it embarrassed him because he had to decide what he was going to do immediately, and could not get back to his office to telephone later what the record showed.

Dr. Asher (closing).—I want to thank Dr. Sprague for his kind criticism. I do, however, want to say that the making of this thing reminds me of the title that Dr. Hertzer first used for "The Horse and Buggy Doctor." The title originally was "Too Dumb to Quit."

I think that sometimes, as we worked with these things, the knowledge of his struggle made us keep on, and perhaps we were too dumb to quit.

Discussion of the paper, "Ligation of Patent Ductus Arteriosus," by Dr. John P. Hubbard, Boston, Mass.

Dr. C. Sidney Burwell, Boston, Mass.—I should like to make two observations concerning this very interesting and important paper of Dr. Hubbard's.

The first is to put on record my admiration for the imagination, determination, and skill which made it possible for these workers to conceive and develop this method of treatment.

The second is to say just a word about one of the points made in the justification of this surgical procedure.

Dr. Eppinger, in my laboratory, has had the privilege of analyzing blood obtained from the pulmonary artery and the adjacent aorta of two of these patients at the time of operation. The analysis of this blood has, for the first time, permitted a demonstration that the shunt, which we all have believed to be present, actually occurs. It has also given us some rather surprising information as to the magnitude of this shunt.

Under the conditions of operation, with the anesthesia and the other phenomena attendant upon operation, in the two patients that have been examined it can be

shown that approximately three-quarters of the blood which comes out of the left ventricle through the aortic valve immediately flows back into the lungs by way of the patent ductus arteriosus.

Such an extraordinary loss of blood from the arterial system can be met in *only* two ways. One way is to subtract this from the peripheral circulation. When that occurs, as Dr. Hubbard suggests, if it occurs over a long period of time, interference in growth may result.

The second way, and, from our observation so far, apparently the main way, is for the left ventricle to increase its output greatly. A great increase in the output of the left ventricle obviously implies a corresponding, or nearly corresponding, increase in the work of the left ventricle, and presumably this explains the limitation which these patients have with respect to exercise and other activities.

It seems to me that these measurements support the contention of Dr. Hubbard, namely, that a patient with a large, patent ductus arteriosus may justifiably be operated upon in an attempt to relieve the heart of this large increase in work.

Dr. William J. Kerr, San Francisco, Calif.—It is indeed a thrilling thing to live in a time when members of our profession have the imagination and the technical ability to perform this operation.

Since last summer, when Dr. Gross performed this first operation for Dr. Hubbard, we have hoped that we would be able to contribute something in this direction. About three months ago the opportunity presented itself to treat a young woman, 26 years of age, who was already beginning to have cardiac failure because of this anomaly. We felt quite certain that there were no other serious abnormalities in the circulatory system. We were bold enough to attempt it, Harold Brown, of San Francisco, performing the operation.

We found, however, that in the adult it may be a little more difficult technically because the ductus lies so deep in the chest. We discovered something which is unusual in connection with this problem. This patient developed collapse of the lung and pneumonia and died subsequent to the operation. At the time of operation, we were not certain that we had tied off the ductus. At autopsy it was found that there was no ductus at all, but that there was a fistula, 7 mm. in diameter, directly between the aorta and the left branch of the pulmonary artery. I think this variation is quite unusual, and it is possible that others like it will be encountered.

I understand that five patients have been treated surgically at the Children's Hospital in Los Angeles by Dr. Dolley, with very successful results in four, and a subsequent complication resulting in death in the fifth.

One of the things Dr. Hubbard brought out, which I would like to emphasize, is that under the fluoroscope one may see tremendous pulsations of the pulmonary artery throughout the entire pulmonary field. This is particularly striking when there is a large fistula.

Another thing of interest is in regard to the murmur. It is said that there is a systolic accentuation of the humming-top murmur in these patients. We have been able to show, however, that this murmur occurs about one-fifteenth of a second after the first sound; this can be brought out by means of the symballophone.

Discussion of the paper, "Changes With Age in the Electrocardiogram in Adult Men," by Dr. Alfred E. Cohn, Dr. William Hall Lewis, Jr., and Dr. A. Garrod MacLeod, New York, N. Y.

Dr. Louis N. Katz, Chicago, Ill.—In regard to this fundamental work, I wish to ask whether or not it is justifiable to include as normal, in such a group, individuals with abnormalities in their electrocardiograms such as prolongation of the P-R or QRS intervals beyond normal limits, or inversion of T₁ or T₂. Until such time that

it is shown that these particular variables can be considered normal, is it not better to consider them, not as normal phenomena of senescence, but rather as abnormalities, even in the aged? After all, at every age abnormalities in the electrocardiograms occur which are not necessarily associated with symptoms and signs. In other words, what is senescence? When is it normal? When is it abnormal? Consequently, I would like to have Dr. Lewis discuss the justification for including the four or five individuals with abnormal electrocardiograms in the normal group of aged persons.

Dr. Lewis (closing).—I should like to answer Dr. Katz's question by remarking first that what we now consider abnormal may, when we have further knowledge about the exact events in senescence, come to be considered normal.

This study has been carried on for some time, and reports have been already published about it. I, myself, was responsible for the selection of a group of men. None was an inmate of an institution. Every one was active. Some of the men (I think I might describe their clinical state to represent how normal they were) had definite histories of activity over long years of life. The oldest man, 101 years of age, was the oldest living Yale graduate. One man, 91 years old, was extremely well known for his investigations, or for his work, as a cartographer with the United States Geological Survey in the West in 1866 and 1867. At the time of his examination, in 1934, he had the preceding summer and the succeeding summer arranged to go out to the Middle West again and retravel the old Oregon Trail.

The observations that have been carried out included not only the electrocardiographic examinations, but also records of blood pressure, urea clearance, and the size and shape of the heart in the telcorontgenogram, in order to give us as much detail as possible about the effects of senescence on the various biologic functions.

In regard to the unusual electrocardiograms, or what have heretofore been considered unusual electrocardiograms, I have some subsequent data on some of these men, and I might make a few points about them.

Let us take one man who was 67 years of age at the time of his examination, in 1934. He was active, healthy, and, according to the various other tests of biologic function, such as the urea clearance and size and shape of his heart, normal. However, his electrocardiogram showed an inverted T_1 , measuring 1.2 mm., and an inverted T_2 , measuring 1.4 mm. He had had no symptoms indicating heart disease of any form, but his electrocardiogram, as I said, showed these abnormalities.

He came for examination, of his own accord, about one month ago when I had an opportunity to see him in my office. He had retired from his official positions in 1934 at the age of sixty-seven. He had continued his many activities, however, in the five years since his examination. He had traveled all over the world on numerous missions as the active head of the International Council of Churches. He said he had never been busier in all his life. He was the former head of the International Y.M.C.A.

Another man who had a prolonged QRS interval, measuring, as I recall, 0.14 second, but who gave no history of cardiac symptoms, has also been very active as a treasurer in the Y.M.C.A. organization for the past five years, and he is perfectly healthy.

On the other hand, there were men who, at the time of the selection of this group, had symptoms of heart disease, such as pain on effort, and yet had normal electrocardiograms. They were not included in the group; not long afterward, it was found that they had died of heart disease.

So, as a matter of fact, it may turn out that certain criteria established by instruments of precision, which we have heretofore considered abnormal, may be, after all, normal when we come to deal with individuals over 65 years of age.

Section for the Study of the Peripheral Circulation

Discussion of the paper, "The Saphenous Valves in Varicose Veins," by Dr. Edward A. Edwards and Dr. Jesse E. Edwards, Boston, Mass.

Dr. Geza de Takats, Chicago, Ill.—I do not feel at all competent to discuss this excellent paper from the histologic standpoint.

Clinicians, of course, have long recognized that the valves in varicose veins are insufficient and that the flow of blood is reversed when the patient is standing. In some previous work, the authors have clearly demonstrated the valvular shrinkage and insufficiency which follow phlebitis. Today they showed with painstaking care, after studying a large number of patients, that in the uncomplicated, noninfected varicose vein the dilatation of the wall is the cause of a relative insufficiency.

Whether this weakening of the wall is due to a congenital defect in the muscular or elastic elements, whether it is due to postural strain on a circulatory system which was originally designed for a four-footed animal, or whether the connective tissue of certain asthenic individuals is such that it gives way more readily to increased venous pressure, cannot be decided by purely morphologic studies.

I believe, however, that one can find evidence for the existence of any one of these possibilities. Thus, in ligating veins at the saphenofemoral junction, one sometimes finds saccular venous aneurysms with a perfectly well-developed muscular wall surrounding them. One cannot help suspecting that there are segmental defects in the wall. In other cases, in spite of marked elongation and dilatation of the saphenous system, there is a pronounced muscular hypertrophy at the upper end of the saphenous vein, which is the normal response to venous hypertension. Again, in other patients, stigmas of an asthenic habitus, such as a long, narrow chest, a sharp costal angle, visceroptosis, and flat feet, signify that we are dealing with a diminished tonus, an inferior make-up of connective tissue.

I should like to ask the authors whether they have found any evidence of absence or rudimentary development of valves in the perforating veins or the femoral vein above the saphenofemoral junction, as described by Turner Warwick. In our clinic we have watched for the incompetence of the femoral valve following straining or coughing and have found it in approximately 10 per cent of all cases. Absence of this important valve above the saphenofemoral junction is said to be found not infrequently at autopsy. It is the only competent valve between the right heart and the saphenous vein. Fluctuations of abdominal venous pressure can be readily transmitted to the lower extremities if this valve is incompetent.

It is to be hoped that the authors will extend their studies to the valves of the iliofemoral veins and, perhaps, also to the sphincters in the caval system, such as have been described in the renal and hepatic veins. These sluice mechanisms open and close a large reservoir, and their varying tonus may be as important for venous return as the valves are.

Their present study conclusively demonstrates that the valvular insufficiency, as far as the upper saphenous valves are concerned, is due to dilatation of the wall of the vessel, and not to local inflammation, degeneration, or rudimentary development of the valves themselves.

Discussion of the paper, "The Mode of Development of Collateral Venous Circulation in the Extremities," by Dr. Ross Veal, Washington, D. C.

Dr. Norman E. Freeman, Philadelphia, Pa.—As before, Dr. Veal has made a very splendid contribution to our knowledge and understanding of the problems of the venous circulation associated with acute obstruction.

I would like to take up this discussion under three headings. The first is the question of the reaction of the blood vessels to the initial closure or the initial thrombosis. That apparently sets up quite a vigorous arterial and venous spasm. Dr. Veal has called attention to the arterial spasm, which may be of such magnitude as actually to cause gangrene. I have observed one patient who has developed gangrene because of spasm following acute venous thrombosis.

Two other patients whom I have seen also developed extremely severe arterial spasm as the result of acute thrombophlebitis.

The second point is the venous spasm. We have been interested, in Philadelphia, in observing these patients with their acute thrombophlebitis, and we have seen unmistakable evidence of acute spasm of the veins in the periphery distal to the site of thrombosis.

Now, our interest in this grew, to a certain extent, out of the observation that, associated with acute thrombosis of the vein, the temperature of the affected extremity frequently was higher than normal. We all recognize the fact that one of the signs of phlebitis is a hot skin. Hot skin means increase in blood flow. Heat must be brought from the body to the periphery and deposited there in order to have the skin hot. We know that the venous pressure is increased, but it is quite interesting that with an obstruction to the venous return there is actually more blood flowing out to the part and, therefore, there must be more blood flowing back from the part.

In view of these facts, there must be collateral venules available even during the acute stage, through which blood could come back from the extremity affected by thrombophlebitis.

We therefore decided, since we knew that blood was flowing out in increased amounts, that by compression of the veins by the application of a tight plaster we would be able to speed up the flow in the channels which were open and prevent stasis of blood in large, dilated veins with very high pressure.

Our results have been just as splendid as those which Dr. Veal obtained by the use of his Unna boot from the toes to the knee. We have used the Ace bandage and bound the extremity from the toes to above the knee.

As far as the character of the fluid is concerned, Dr. Veal spoke about the fact that when the lymphatics are blocked an increase in edema formation occurs. One other fact should be mentioned, namely, that when there is an inflammatory reaction of the tissues in the lower leg, as, for instance, after acute thrombophlebitis, there will be an outpouring of fluid which is rich in protein. The blood vessels are damaged, and when the fluid is examined, one finds that the protein content is between 2 and 4 per cent. That is subcutaneous fluid in the area of tremendous edema, after an acute thrombophlebitis.

If we can prevent those vessels from releasing this protein-rich fluid, we will do much to decrease the fibrosis and resultant incapacity after the period of recovery.

Dr. Geza de Takats, Chicago, Ill.—There are certain points in Dr. Veal's excellent paper which I believe should not go undiscussed. One is the sudden increase in venous pressure on exercise in cases of axillary thromboses. These patients have definite intermittent "claudication" of the upper extremity when they exercise their arms. It seems to me that the high venous pressure would be capable of explaining that.

In the lower extremity, the intermittent claudication is usually regarded as an indication of impaired arterial circulation, but when a patient with axillary thrombosis exercises his arm, the pain becomes, very shortly, unbearable. We have observed that again and again.

Another point is that this edema must be due, at least in part, to certain vascular reflexes originating from the thrombosed vessels. In two instances, in patients who

had been in bed with the arm elevated, we were able to get rid of this edema after stripping the thrombosed vein, an observation which, of course, has been made by Leriche and others.

The most important point, however, I think, is the idea that these patients with a deep thrombophlebitis can get up in a few days. Dr. Veal did not make it quite clear, and I wish to ask him just when he allows them to get up. Certainly he does not let them stay in bed for four or six weeks. In a few cases we have allowed these patients to get up, wearing their elastic support from the toe to the groin.

It is my impression that the incidence of embolism is certainly not higher in this group than it is among the patients who are made to stay in bed for a long time.

In a recent survey of our cases of pulmonary embolism, we found that in only 2 out of 100 was there a frank, deep thrombophlebitis. Therefore, it seems to me that, if a patient should have pulmonary embolism after getting up early, the chances are that he would have had it under any circumstances. In fact, our two patients who did develop pulmonary embolism were immobilized for as long as eight weeks.

Dr. Irving S. Wright, New York, N. Y.—It has been our observation that allowing patients with thrombophlebitis to be up and about has aggravated the local symptoms in many cases, even though embolism did not seem to occur oftener. This seems more likely to occur when the superficial veins are involved.

I would like to ask Dr. Veal's opinion regarding this.

Dr. Veal (closing).—I am of the same opinion as Dr. de Takats, namely, that these patients should be gotten out of bed very promptly. In most of these cases the patient has been operated on, and one must therefore wait until the post-operative course is at such a stage that he may be allowed out of bed with safety.

As for the local symptoms, if the boot is placed high enough and firm enough we have not yet found that it has caused any pain or increase in other symptoms. It seems that the heat kept in by this boot tends to release the spasm of the arteries and veins, and it certainly lessens the edema.

One other point I did not bring out. During the acute stages, before one can let the patient out of bed, there are likely to be increased edema and some cyanosis. We have found that alternating the position of the bed tends to relieve this edema and cyanosis. We elevate the foot for an hour and then reverse the procedure and elevate the head. It certainly brings about some relief and prevents the formation of too much edema.

Discussion of the paper, "The Significance of Vascular Hyperreaction, as Measured by the Cold-Pressor Test," by Dr. Edgar A. Hines, Jr., Rochester, Minn.

Dr. Irvine H. Page, Indianapolis, Ind.—Dr. Hines has, I think, developed an impressive body of evidence in the past six years. The effort to estimate the responsiveness of the vascular system by some method such as the cold-pressor test has always seemed to me to be desirable. Among the many methods proposed, none seems to be simpler than Dr. Hines' test. Probably it is actually a combined cold and psychic stimulus, because immersion in water at 4° C. is quite painful. I have seen many patients complain bitterly of the cold when the hand was immersed in ice water.

Obviously, the important question to be answered is whether or not, in fact, the cold-pressor test enables us to predict the development of hypertension. In favor of this opinion is chiefly the observation that more cases of hypertension occurred

in the small number of hyperreactors originally studied by Hines and Brown than in the hyporeactors. As Hines points out, we shall have to wait ten years before this can be conclusively established.

It is alarming to hear that if both parents are hyperreactors, 95 per cent of the children react similarly. This would almost surely doom the children to hypertension. I think Dr. Hines would agree that, while this may be the trend, it by no means necessarily seals the children's fates. I have, and doubtless the rest of you have, seen persons, both of whose parents had hypertension; yet they were without a sign of it. In one family I watched for its appearance confidently for seven years, with no success, although the children had entered the fourth and fifth decades.

It is needless for me to point out the importance of this work. It is worth suggesting that physicians apply this test to large groups of patients who can be followed from year to year, so that the question of whether or not this test foreshadows the future may be answered definitely. But under no circumstances should the patient be told the result. Perhaps the result should be sealed in an envelope, like election predictions.

My personal feelings are mixed, regarding this test. I have employed it with varying success. Now that I have seen Dr. Hines' figures, I sense that the burden of proof is gradually being shifted to the disbelievers. Whatever one's personal opinions in the matter, sufficient evidence has been presented to demand an unequivocal answer, and the rest of us should lend a helping hand.

Dr. John H. Miller, New York, N. Y.—Last year Dr. Maurice Brugger, of New York Postgraduate Hospital, and I became interested in the possible application of this cold-pressor test as a clinical method for differentiating essential hypertension from the secondary forms of hypertension, particularly the type seen in chronic renal disease.

A group of normal hypo- and hyperreactors was also studied for purposes of statistical evaluation. We followed the procedure of the test as outlined by Dr. Hines, except that we used a recording sphygmomanometer instead of the auscultatory method. I will not go into all of our results, as they will appear later in the *AMERICAN HEART JOURNAL*, but the responses of our normal hyporeactors and hyperreactors, as well as of the patients with essential hypertension, closely paralleled and confirmed the observations of Dr. Hines.

One not infrequently encounters a patient with hypertension and urinary abnormalities, in whom it becomes very difficult to determine whether the elevation of blood pressure is due to kidney damage, or vice versa.

In our patients with proved nephritis, 73 per cent of whom had hypertension, we found that the mean response to the cold stimulus was 16.2 mm. in systolic, and 12.6 in diastolic, pressure. These figures, though slightly above the mean response of the normal hyporeactor group, showed no appreciable deviation when compared statistically. I note that they are within 1 mm. of the mean response for the entire normal group given by Dr. Hines.

While we were carrying on our studies, Allen and Smirk reported their results with this test and showed that, unlike most patients with essential hypertension, patients with nephritic hypertension do not exhibit a hyperpressor response to cold; however, their patients with renal hypertension gave a response lower than the normal hyporeactor group.

In view of this work and our results, we concluded that a hyperreactor response in a patient with arterial hypertension would exclude chronic renal disease as the cause.

We do not feel that the converse of this holds true, as we found that 24 per cent of our patients with essential hypertension gave a response within the limits of normal. This group must be the subject of further investigation.

In order to determine, if possible, the factors causing this lack of hyperreactor response in some patients with essential hypertension, we subdivided this group according to the degree of arteriosclerosis present, the presence or absence of albuminuria, the duration of hypertension, and, finally, according to age.

It was found that those individuals exhibiting moderate to severe degrees of arteriosclerosis, those having albuminuria and secondary manifestations due to nephrosclerosis, and, finally, those between the ages of 65 and 75, had an appreciably smaller response to cold than did those who had few or none of these complications or were younger.

However, we do not feel that these factors alone account for the lack of a hyperreactor response in some patients with essential hypertension.

As Dr. Hines has stated, it will take another ten or twenty years to ascertain whether or not essential hypertension occurs among the present normal hyporeactor group. Should this occur, we feel that it may possibly explain the small percentage of normal responses encountered in the essential hypertension group.

Dr. Hines (closing).—I appreciate Dr. Page's and Dr. Miller's discussions of my paper. I agree with Dr. Page that the general use of the cold-pressor test to predict the future development of hypertension is not indicated at the present time. As I stated previously, the main purpose of this presentation was to show that a prehypertensive, or an antecedent stage, of essential hypertension exists. Unquestionably, it will take another five or ten years to determine definitely how many of the hyperreactors will develop essential hypertension. Furthermore, the test does not indicate when hypertension will appear or how severe it will be if it does. I think that we have enough phobias without adding the phobia of high blood pressure.

My experience with the test in patients with chronic nephritis, although more limited than that of Dr. Miller, is similar to his. I have not found the reactions in patients with renal disease to be as marked as in those with essential hypertension.

Discussion of the paper, "The Cardiac Factor in Experimental Vasomotor Hypertension," by Dr. Norman E. Freeman and Dr. W. A. Jeffers, Philadelphia, Pa.

Dr. J. Murray Steele, New York, N. Y.—I have only one or two words to say. It is an extraordinarily interesting piece of evidence for the existence of a choice of innervation in an organ; without adrenalin, the sympathetic nerves seem to be able to do for the heart what it needs; without the sympathetic nerves, adrenalin seems to be able to arouse the response.

There is a large number of factors involved in the hemodynamics of this situation. Decrease in tone of the heart muscle, whether due to lack of adrenalin or to failure of the nervous mechanism, might prevent the output of sufficient amounts of blood to give rise to hypertension. Or, decrease in tone of the splanchnic vessels, due to either of the two mechanisms, might prevent the return flow to the heart to such a degree that high arterial pressure could not be maintained.

I noticed that the rate did increase in somewhat similar fashion to the increase observed by Heymans. One needs very badly to know also whether cardiac output changed, before deciding precisely what mechanisms are involved.

One would like to know, also, whether, under the circumstances under which hypertension does not occur, stimulation of the carotid sinus mechanism has the same effect as when nerves of the heart have not been operated upon.

There are some experiments of Barcroft that are of interest in this connection, too. One can imagine that the whole reaction, the whole development of hypertension, might take place in the first few beats of the heart. If the aorta is abruptly clamped, there is an immediate and sudden pressor response, which dies off gradually in the course of forty or fifty minutes. That rise in pressure can be completely inhibited if the return flow from the splanchnic region is cut off by clamping, at the same moment, the inferior vena cava. Suppose, then, that some change occurred in the heart or in the great veins to prevent increase in the return flow during the first few beats; the immediate large increase in pressure might never occur.

I should like very much to know whether Dr. Freeman has measured cardiac output, and whether he has tested the response to the carotid sinus mechanism.

Dr. Freeman (closing).—We have attempted to measure cardiac output with the ballistocardiograph of Dr. Starr and have observed in normal dogs that there is a marked increase in the force of ejection.

It is difficult to analyze exactly what happens after operations have been performed on the dog, but it does modify the reaction. I think that Dr. Steele has put his finger on the crucial point which is involved in consideration of this form of hypertension, and that is the question of the cardiac return, the return flow of blood to the right heart.

According to Starling's concept, the heart will put out whatever blood it receives, independent of the peripheral resistance, so that, with a given return of flow to the right heart, the pressure will vary directly with the peripheral resistance.

On the other hand, as the peripheral resistance is increased, unless the cardiac output is maintained constant, there will be a decrease in blood flow, because, as the resistance is increased, provided there is not a rise in blood pressure, the return flow will be diminished.

It seems to us that the failure to obtain hypertension in this experiment is probably ascribable to a deficiency in cardiac output. That is, the peripheral resistance increases but the return flow of blood to the heart is diminished.

I thank Dr. Steele very much for his discussion.

Discussion of the paper, "The Effect of Heparin in the Prevention of Thrombosis Experimentally Produced in Various Blood Vessels," by Dr. D. Y. Solandt, Dr. R. Nassim, and Dr. C. H. Best, Toronto, Canada.

Dr. Irvine H. Page, Indianapolis, Ind.—The results which Dr. Solandt, Dr. Nassim, and Dr. Best report leave no doubt about the effectiveness of heparin in preventing the thrombosis which is ordinarily produced by sodium ricinoleate. It is probably not too much to suppose that it will be equally effective in preventing thrombosis from other causes.

The method used for producing thrombosis is an interesting one. I should like to ask whether other, simpler, soaps also produce thrombosis. Dr. E. V. Allen and I (*Arch. f. exper. Path. u. Pharmacol.* 152: 1, 1930) found that the ricinoleates were the most toxic of all the soaps we studied, that the highly unsaturated soaps were next, and that the saturated soaps were least toxic. Can you explain the mechanism of thrombus formation by soaps?

Obviously, a most important question is whether or not heparin can be employed therapeutically to arrest thrombus formation. Certain evidence indicates that it can, and Dr. Best and his associates can tell you of this better than I, because I know that they have been concerned in several of these attempts. It has gradually come to be realized that thrombi do not form instantaneously, so that there is time to arrest the process if it can be detected. That heparin can arrest it seems clear from the results we have just heard reported. Two problems immediately arise:

1. Is heparin the best anticoagulant for the purpose? 2. Can the diagnosis of early thrombus formation be made early enough? My belief is that heparin is, so far, the best, though by no means the cheapest, anticoagulant.

Synthetic substitutes for it may soon be found. Certainly a start has been made in the early diagnosis of coronary thrombosis. I need only cite Dr. Kerr's recent work. Since the work of Dr. Solandt, Dr. Nassim, and Dr. Best has done the important service of calling attention to the necessity of early diagnosis by placing a therapeutic tool in the hands of the physician, there will doubtless be a rapid advance in the efficiency of our diagnosis. The opening of new vistas in medicine, such as this, should give us pride in clinical investigation.

Dr. Arthur M. Master, New York, N. Y.—One cannot emphasize too much how important heparin may prove to be. We had occasion only yesterday to report that, in our post-mortem examinations of patients with coronary occlusion, almost half showed mural thrombosis and that embolism therefore was frequent. Perhaps heparin may prevent all this.

Another way of emphasizing the importance of the problem is to tell you that we now have a paper in press in which, with the help of board of health agencies, we have shown that at least half a million attacks of coronary occlusion take place yearly in this country.

Now, in regard to the premonitory symptoms, it has been reported that as high as 50 per cent of the patients do have premonitory symptoms. So, it may be possible to use heparin before occlusion has actually occurred. Certainly, it might be important to use heparin in those who suddenly develop a severe anginal syndrome due to coronary sclerosis.

I have not had any experience with the acetylcholine method of producing coronary thrombosis, so that the questions I raise are entirely theoretical. Dr. Solandt brought out that the mode of occlusion here is apparently different from that which takes place in man. In the latter, as you know, occlusion usually occurs as a result of intimal hemorrhage, whereas here it is really a clot formation on injured endothelium.

My last point is this: I wonder whether or not it would be worth while to take older dogs, who have, perhaps, coronary sclerosis, tie off a coronary artery, and then, after two days, or, perhaps better still, in the second week, give heparin and see whether it will prevent mural thrombosis and embolism.

Dr. John J. Sampson, San Francisco, Calif.—In confirmation of what Dr. Master has just stated, I wish to make a brief comment. Approximately two years ago, both Dr. Feil, of Cleveland, and Dr. M. Eliaser and I, in San Francisco, reported series of cases in which it was shown that in approximately 50 per cent of the cases of coronary artery occlusion the onset could be predicted by the occurrence of a certain, definite, premonitory symptom. This was persistent pain, which was not relieved by nitrites and was not followed by any of the recognized characteristics of acute coronary occlusion, such as, most particularly, the leucocytosis, increased erythrocyte sedimentation rate, or fever. There were no electrocardiographic changes in the majority of our cases.

It was felt, in discussing this syndrome with Dr. Feil recently, that perhaps these were instances of subintimal hemorrhage which later extended sufficiently to produce completely occlusive arterial thrombosis. Whether or not we can prove this pathologically remains to be demonstrated.

Dr. Chester M. Kurtz, Madison, Wis.—I think there is no question that heparin may now be regarded as a very potent drug in combatting thrombosis. However, there is one important precaution to be observed, namely, that one should carefully

differentiate between thrombosis and hemorrhage, particularly in cerebral accidents, before administering this preparation. In the presence of thrombosis, heparin is definitely indicated, but if one is dealing with hemorrhage, the condition may be aggravated rather than helped.

As has already been proposed by others, heparin may prove of value in the treatment of subacute bacterial endocarditis. There is reason to expect that some derivative of sulfanilamide will be developed which will have the power of destroying the *Streptococcus viridans* in the blood stream. If some drug such as heparin could be depended upon to inhibit or prevent the formation of the thrombotic vegetations on the heart valves which are known to protect and promote the growth of the organisms, there is a possibility that the infection might be overcome. Even if the heparin had to be given continuously over a period of time, it might prove of value and possibly provide another weapon against this disease which, at the present time, is fatal in practically 100 per cent of all cases.

Dr. Irving S. Wright, New York, N. Y.—We have had occasion to utilize heparin, and I should like to mention one experience which we had because I think it might be of interest to the audience as a whole.

This was in a patient with migratory thrombophlebitis, an individual who had had a fever for four or five months without amelioration from any form of therapy which we had been able to utilize, until we started with heparin.

We gave him heparin for twelve consecutive days intravenously, according to Dr. Best's own directions. During that time his temperature dropped to normal; in fact, it dropped to normal within six hours of starting the heparin and remained normal during the twelve days and for ten days thereafter.

After that period of time the temperature again began to show an irregular upward trend, which has persisted to date (many weeks). On the second attempt with heparin, about three weeks later, no effect whatever on the fever could be demonstrated.

There seemed to be no question that within a few hours of the original administration there was a heparin effect which persisted for the twelve days of administration and for ten days thereafter.

As noted, we were unable to repeat this experience, and I would like to hear Dr. Solandt's reaction on this matter.

Dr. Solandt (closing).—Putting the last first, I think it is a common experience that the fever caused by thrombophlebitis does very regularly drop quite soon after commencing the administration of heparin. We have no idea why this is so, because, as far as we have been able to discover, heparin has absolutely no effect on clots already formed. It prevents the further extension of the thrombus but has no effect on that already formed. I have no idea why the fever was dispelled in the first instance and was not affected in the second.

Coronary occlusion in old dogs will not, with any degree of certainty, bring about mural thrombus formation. We thought that it probably would, and we tested this idea in a number of old dogs by simply tying the coronary arteries. We obtained no mural thrombi.

I am very much interested to learn that so many physicians find useful premonitory signs associated with coronary thrombosis. The clear recognition of such signs will greatly facilitate the application of heparin to the treatment of this condition.

The cost of heparin is certainly a drawback to its use. At present, to heparinize a patient adequately about doubles the cost of hospitalization. In Canada it costs from four to seven dollars a day to keep the clotting time around twenty minutes. I believe that at present heparin is not made in the United States, so that you

would add 60 per cent to that figure. That possibly suggests a simple way by which you might reduce the cost of heparinization.

Discussion of the paper, "Activation of Renin and Its Vasoconstrictor Properties,"
by Dr. Kenneth G. Kohlstaedt, Dr. Irvine H. Page and Dr. O. M. Helmer, Indianapolis, Ind.

Dr. J. Murray Steele, New York, N. Y.—I can add very little to this really beautiful piece of work on a substance which has recently been investigated with increasing interest. Since the time of Tigerstedt and Bergmann, all of the work combined has served chiefly to show that renin can be quite regularly recovered from normal renal tissue. It has also been purified to a much greater extent.

But the discovery that it was not simply a single, simple substance, apparently manufactured by the kidney, with a direct constricting action on the peripheral arterioles, has revolutionized our thinking about the matter. We no longer think in such simple terms. We have to consider enzyme systems; we have to consider the possibility that two substances may have to combine in order to act. The possibility also exists that the absence of a substance which normally counteracts the action of renin must be considered. But, at any rate, it has distinctly changed our whole manner of thinking about renin.

It seems almost impossible that such a very potent substance can be present in normal renal tissue in much larger amounts without having a certain significance. One may think of it as supplying a long-range regulation of blood pressure, for it is not likely that pressure is ordinarily maintained by stimulation of the sympathetic nerves or by the constant inflow of adrenalin.

Perhaps such a substance that acts a little more slowly, whose action is a little more persistent and so well distributed over the whole arterial musculature, is the basis, the background, for the regulation of normal blood pressure upon which regulation by nervous mechanisms and adrenalin is superimposed.

It is at the moment difficult to link renin directly to hypertension, but this paper of Dr. Kohlstaedt, Dr. Page, and Dr. Helmer removes one more objection to doing so.

There are one or two questions I should like to ask. Have you attempted to inject plasma or purified renin separately in order to determine the time necessary for the two to react, that is to say, perfusing with serum present, then injecting a small amount of renin, and vice versa? How long after one is injected can you inject the other and obtain an effect? That might give some information as to the way these two parts of the whole interact.

I should like to congratulate Dr. Kohlstaedt, Dr. Page, and Dr. Helmer on this remarkable addition to our knowledge of renin.

Dr. Norman E. Freeman, Philadelphia, Pa.—Since the kidney has been identified by Goldblatt as the cause of the rise in blood pressure associated with clamping the renal artery, a series of different concepts has evolved.

First, there is the question of a pressor substance, which was not excreted. Then there is a pressor substance which is normally formed in the kidney and is normally excreted, but is not excreted when the renal artery is clamped. Recently, T. R. Harrison has suggested that normal kidney has an antipressor substance.

I think one of the most interesting and most suggestive concepts is the one which these investigators, Dr. Kohlstaedt, Dr. Helmer, and Dr. Page, have suggested today. We know that there is a substance, renin, present in the kidney, and the possibility that a coactivator is increased with disease of the kidney is, I think, extremely suggestive.

There is one question I would like to ask Dr. Kohlstaedt. He has mentioned vasoconstriction in the dog's tail. Studies on renin at other laboratories seem

to indicate that a rise in blood pressure is produced in an intact animal when renin is injected, but there is not a preferential vasoconstriction in the periphery.

I wonder if Dr. Kohlstaedt can explain how he harmonizes this observation with his findings.

Dr. Alberto C. Taquini, Buenos Aires, Argentina.—We have found a pressor substance in the plasma of blood from an ischemic kidney, as in the experiments described. This was not present in normal plasma. When normal plasma is made of chemical substances, in order to separate the globulin and albumin, the pressor substance appears.

I am wondering if the renin dialysate, mixed with normal plasma, may produce these substances, which I feel are different from those liberated by the ischemic kidney.

Dr. Myron Prinzmetal, Los Angeles, Calif.—I wish to congratulate these workers on this very beautiful and important work. I should merely like to ask whether they have examined renal-vein blood of the ischemic kidneys of hypertensive animals to see whether the activator is present in increased quantities.

Also, I would like to point out that Dr. Ben Friedman and his co-workers have done similar experiments, but I think they came to the same conclusions. Friedman perfused an isolated dog's tail with plasma, plus renin, and obtained a constriction of the vessels of the tail, but when he perfused the tail with Ringer's solution, or with saline, he did not obtain any constriction at all.

Friedman's observations agree very well with those reported here today.

Dr. Louis N. Katz, Chicago, Ill.—I want to add my congratulations to those of the previous speakers. I think, for the first time, we have a way to explain why the substance first described by Tigerstedt and Bergmann might operate in the production of hypertension.

The results with renin are coming so fast from so many places that I think the question of priority nowadays, with modern transportation, radio, and, soon, television, need no longer concern us.

It is interesting that the observations just hinted at in this report, regarding the fact that renin is apparently not a sympathomimetic substance, we have been able to confirm in our laboratory.

I wish to know whether the authors have attempted to correlate this activator substance with the adrenal gland. They discussed the hypophysis, but there is still a controversy about the role of the adrenals. Is it possible that this coenzyme, or activator, or additive substance, comes from the adrenals?

Dr. Kohlstaedt (closing).—I wish to thank all the discussers. I will do my best to answer the questions, although some will be rather difficult because, as you all have seen, we have only begun our work. We feel that this method is still rather inadequate for close quantitative comparisons.

In answer to Dr. Steele's question, we have found that after long, repeated injections of renin, we were able to inject the plasma alone and produce vasoconstriction.

I am unable to explain fully Dr. Freeman's question. Vasoconstriction, which is not shown in the experiments, may be produced in parts of the body by renin.

In answer to Dr. Prinzmetal's question, the renal-vein blood has been studied, but we do not feel that we have carried on enough experiments to say that this blood contains less of the activator than the peripheral blood.

In answer to Dr. Katz' question, we have studied adrenalectomized animals, and find adrenalin present, but whether it is altered in quantity we are not certain.

Discussion of the paper, "The Effect of Deproteinized Pancreatic Extract in the Treatment of Intermittent Claudication in Arteriosclerotic Peripheral Vascular Disease (Intramuscular and Intravenous Administration)," by Dr. A. Wilbur Duryee and Dr. Martin Fisher, New York, N. Y.

Dr. Nelson Barker, Rochester, Minn.—Carefully controlled experiments by a number of different investigators have demonstrated that several different types of tissue extracts, when administered intramuscularly to human beings, exert an inhibiting effect upon the symptom of intermittent claudication. In general, this effect is inversely proportional to the degree of arterial insufficiency.

Unfortunately, we know relatively little concerning the exact constituent of these extracts which is responsible for the effect on intermittent claudication. It is an open question whether the present method of standardization of these extracts has anything to do with the anticlaudication factor. Efforts to demonstrate vasodilatation in human beings following intramuscular injection of pancreatic extract have failed, even though a definite inhibitory effect on intermittent claudication has been observed in the same individual during the same period.

It is possible that the factor in the extracts which inhibits intermittent claudication acts directly upon the muscle itself, or on the metabolism of the muscle, rather than indirectly through an increase in the flow of blood. In support of this concept is the observation that in a few cases of myasthenia gravis, intramuscular injections of tissue extracts have resulted in definite improvement of muscular strength and tone. Therefore, I think that there are definite objections to standardizing any of these preparations, including the deproteinized pancreatic extract, on the basis of inhibition of the vasoconstriction effect of epinephrine.

I should like to congratulate Dr. Duryee on his excellent, well-controlled experiment on a condition which does not readily permit of controlled experiments. At The Mayo Clinic we have used deproteinized pancreatic extract in a limited number of cases and, in general, our conclusions regarding its effectiveness are in agreement with those of Dr. Duryee.

One very obvious advantage of the aforementioned extract over other tissue extracts which have been used in the treatment of intermittent claudication is the fact that it does not produce pain at the site of injection. A second obvious advantage, as Dr. Duryee said, is the fact that the removal of the protein from the extract apparently removes the danger of systemic reactions. It appears that deproteinized pancreatic extract has just as good an effect on intermittent claudication as any of the other tissue extracts, and that it therefore represents an advance in this type of therapy.

Dr. Joseph B. Wolfe, Philadelphia, Pa.—The interesting work presented by Drs. Duryee and Fisher will aid greatly in determining the therapeutic value of pancreatic extract.

In 1929, when we first published a paper on the therapeutic application of an extract prepared from the pancreas, we were of the impression that extracts of all tissues had similar effects, and suggested the name "Tissue Extract," which we have used in subsequent publications. Further studies revealed that whereas similar extracts of various tissues have properties which are common to all, they also have properties which are specific for each particular tissue. In addition, it is also well to designate specifically the method of extraction, as well as the particular tissue employed, since different methods of preparation produce extracts with different properties.

The clinical employment of this particular type of pancreatic extract was suggested by the following observation: Dr. Vaquez, of Paris, noted that the stenocardia

of diabetic patients was greatly benefited when impure insulin was used. Thus, in addition to controlling the diabetes, he was able to relieve a great many of the patients of attacks of angina pectoris. When he used purified insulin, he found that not only did he fail to relieve painful cardiac failure, but that a great number of the patients developed anginoid attacks while under treatment.

Impressed by these observations, I felt that there must be an important by-product which was being discarded during the manufacture of insulin. With the aid of Sharp and Dolme's chemists and pharmacologists, we were able to prepare a fairly potent and moderately well-standardized preparation which we called "Tissue Extract No. 56S." In this insulin-free pancreatic extract we found one fraction which has hormonal qualities, is parasympathicotropic, neutralizes epinephrine, and, whether alone or in combination with another fraction, influences lipid metabolism.

Time will not permit me to mention many other pharmacologic properties which this extract possesses. We believe that the therapeutic value of pancreatic extract is the result of its influence on fat metabolism and its ability to neutralize epinephrine. We have also shown (at the Physiological Congress in Rome, in 1932, and again in Leningrad, in 1935) that if this substance is administered for a long period of time the blood-fat level falls. The deproteinized pancreatic extract which Dr. Duryee is using is simply Tissue Extract No. 56S in slightly purified form.

Judging from our studies, the best results obtained with this particular pancreatic extract (desympatone) are in cases of atheromatosis. Whether the lesions predominate in the vessels of the lower extremities, the coronaries, the aorta, the brain, or the kidneys makes very little difference. We look upon atheromatosis as a sequela of disturbed lipid metabolism, most commonly secondary either to hepatic or pancreatic disease. Therefore, whether we are dealing with intermittent claudication, angina pectoris, visual disturbances, transitory hemiplegias, or any other symptom caused by an impairment of the circulation, if it is caused by atheromatosis we would expect to benefit the patient by administering this pancreatic extract, since by so doing we are attacking the underlying etiologic factor.

It is important to bear in mind that the preparations on the market are not as yet standardized carefully enough. Etiologic factors should be considered carefully, and pancreatic extract should not be used indiscriminately in all circulatory disturbances. Improper employment of the substance may lead to seemingly contradictory results and discourage investigators from studying this important subject.

We are at present investigating the effects of various fractions of pancreatic extract and have been fortunate in enlisting the cooperation of members of the Biochemical Division of the Franklin Institute. I feel certain that a very important substance will be isolated which will aid greatly in the prevention and treatment of atheromatosis.

Drs. Duryee and Fisher should be congratulated on their continued efforts in the application of a new remedy.

Dr. Duryee (closing).—I want to thank Dr. Barker and Dr. Wolfe for their excellent discussion of this subject. We realize only too well that the real action of this substance or substances (there is probably more than one in these extracts) is not known, and we are hoping that the next two years will see a considerable amount of work done in various research centers on this subject, so that perhaps we may obtain a substance that can be easily and readily standardized, such as insulin.

Discussion of the paper, "Effect of Estrogenic Substances Upon Vasomotor Instability in Human Extremities," by Dr. Louis G. Herrmann, Cincinnati, Ohio.

Dr. Kenneth Thompson, New Haven, Conn.—I feel somewhat apologetic in discussing Dr. Herrmann's paper, since he has had such wide experience in these matters, whereas I have only recently begun to study the peripheral vessels.

Having devoted the last five years to a study of endocrine glands, perhaps I can make a few suggestions in regard to therapy. I think the first thing to decide is whether the endocrine therapy is directed toward the primary cause of the malady or toward symptomatic relief.

I think that almost every endocrinologist would agree that the estrogens or other sex hormones probably have some effect upon the peripheral vessels, especially those of the skin. There is a good deal of evidence from various sources to support this statement, as illustrated by the following observations: the blushing of the newborn infant is thought to be caused by the extremely high estrogen content of the mother's and baby's blood at the time of birth; it has been demonstrated recently that the skin of eunuchoid men has a greater circulation of blood following androgen therapy; likewise, I think reliable experiments have demonstrated that the peripheral circulation is increased with estrogenic therapy.

Dr. Herrmann's main point, I believe, is that with estrogen therapy his patients with peripheral vasospasm have found benefit. I think the facts he presented are sufficient to warrant a further study of this form of therapy. These investigations, I think, should be carefully controlled with observations of the endocrine glands as well as of the peripheral vascular system. For instance, in the case of women we are able, by means of the endometrial biopsy, to obtain a fairly accurate estimate of exactly what activity is going on in the uterus and in the ovaries. We can tell whether the patient ovulates and produces a corpus luteum, or whether she doesn't. Whether the corpus luteum was acting in concert with the estrogens in Dr. Herrmann's experiments we do not know. Such endometrial studies should be carried out in his patients, in addition to the carefully controlled studies of the peripheral circulation.

I have not treated any patients with estrogens, but I have treated some with the androgen, testosterone propionate. I became interested in it because, two years ago, I started treating a eunuchoid man of twenty-eight with testosterone, and in the course of a year found that his calf muscles began to hypertrophy. At about that time I was also working in the peripheral vascular clinic, and found that some of my patients were elderly men with claudication and cold feet, and that they also were impotent. Their impotence was of four, or five, or six years' duration. Treatment of four of those patients, upon whom I could obtain reliable, constant-room-temperature studies, with oscillometric measurements, has brought about remarkable subjective and objective improvement.

I think that in those particular cases the deficiency is perhaps primarily in the hormone which has some important primary effect upon the blood supply of muscle and skin. I am not so sure whether such may be the case in these other types of peripheral vasospasm under discussion today. I do not think any of these questions can be settled until we carry out more studies of the type that have been proposed today.

Dr. Irving S. Wright, New York, N. Y.—I should like to remind Dr. Herrmann that we are always interested in knowing what other treatment the individual is subjected to at the time that experimental therapeutics are being undertaken.

One of the most difficult problems we have in the field of the peripheral circulation is the evaluation of any form of therapy. When individuals are put on a regime which includes abstinence from smoking, are given hot baths, and when their

whole environmental temperature is changed by wearing heavier clothes and warm socks, it sometimes greatly confuses the issue.

Therefore, we always have to take these factors into consideration. I should like to hear from Dr. Herrmann how they were controlled in this series of cases.

Discussion of the paper, "The Use and Value of the Vasoscillator in Diseases of the Peripheral Arteries," by Dr. C. E. Sanders, Kansas City, Kan.

Dr. Samuel H. Sedwitz, Youngstown, Ohio.—We all know about the Buerger-Allen exercises in the treatment of peripheral vascular diseases, and of various appliances made to help change the position of the leg and avoid muscular fatigue and tiring of the patient.

Years ago I had a railroad worker who devised a scheme of placing his leg in a hammock, suspended on a pulley, with counterweight, and at the same time saved himself the trouble of actually lifting the leg. I believe Dr. de Takats started the combined use of elevation of the leg and intermittent venous occlusion. Many men in Europe employ the same methods.

With respect to this oscillating bed, one has to employ it only a short while to appreciate the valuable contribution that Dr. Sanders has made in the therapy of the peripheral vascular diseases. In combination with intermittent venous occlusion, especially, one finds that it saves the trouble of shifting patients from their beds to receive the various other treatments, and when suction-pressure treatment is indicated, one can apply the boot when the bed is level and keep it level, especially when the treatment is applied for only a few hours.

Furthermore, in our clinic we have not only been using a heat cradle with thermostatic control (100° F.), but also, to conserve this heat, and prevent the loss which occurs when the bed pan is used or blankets lifted, we cover the involved extremities with a layer of paraffin which is wrapped up in an oilskin bandage. Since adopting this procedure we have noticed that the patients were relieved of their claudication and rest pain much more quickly.

Furthermore, not only has this bed proved satisfactory in our hands for the treatment of peripheral vascular diseases, but we have used it in cases of osteoporosis, nonunion of fractures, arthritis, and postoperative thrombophlebitis.

One particularly outstanding case was that of a man who sustained twenty-two fractures in various parts of the body—ribs, clavicle, scapula, both arms, pelvis, both femurs—and had no union at the end of nine and one-half months; in fact, he was about to receive roentgentherapy for parathyroid disease. After seven weeks' continuous treatment with this bed (he had not been able to move, and could hardly turn to bathe properly) he is back at his work as superintendent in a steel mill. He is walking perfectly except for a partial ankylosis of his ankle, which is aided by a brace.

Furthermore, in cases of Buerger's disease in which suction-pressure treatment provoked more vasospasm, we found that the oscillating bed would sometimes relieve the pain within forty-eight hours, whereas formerly, when we used only intermittent venous occlusion, if the symptoms were mild and the patient stopped smoking entirely, we succeeded occasionally in relieving the pain within 4 to 7 days. Invariably, these patients feel better, sleep better, eat better, and will cooperate more.

In the old arteriosclerotic cases, in which there are rest pain and claudication, the bed has proved very satisfactory, because the patient rests and the work of his heart is reduced to a minimum. When they are tired, or if the noise of the motor disturbs them somewhat, they touch the button and leave it off. They are easily fed and cared for generally. In cases of embolic occlusion, of which we

have had eight, the results have been satisfactory, with loss of pain due to vasospasm, and no local morbidity except in one case. Of course, about 50 per cent of these patients would have recovered spontaneously, without any resulting gangrene or permanent disability. When we would ordinarily give papaverine intravenously every four to six hours for two or three days, for relief of pain, only one to three doses were required when the bed was used. The legs would get warm within six to twenty-four hours. In one instance the patient had emboli at both iliac bifurcations; both legs were involved, but he lost only one (left), below the knee. This is the only patient who did not respond.

As was stated in a previous paper, shifting a patient with thrombophlebitis was helpful. We use the bed and find it most beneficial. The edema disappears sooner, i.e., in a week or ten days.

The chief advantage of the bed is that it enables us to improve the patient's peripheral circulation without any effort on his part.

Dr. Nelson Barker, Rochester, Minn.—At the Mayo Clinic we have been using oscillating beds in the treatment of occlusive peripheral arterial disease for three and a half years. Our experience with this type of treatment, based on results in eighty-eight cases, can be summarized as follows: There seems to be little difference in its effect on the various types of peripheral arterial disease when there are essentially the same degree of arterial insufficiency and the same type of pain. We have observed little or no effect on intermittent claudication. The most striking effect has been the relief of retropathic pain, of the pain of ischemic neuritis, and of the pain caused by ulceration and gangrene. This relief of pain is not necessarily maintained when treatment with the bed is stopped. Skin temperature tests have showed that treatment with the vasoscillator usually produces some vasodilatation, but that this is usually not complete. There is also some increase in oscillometric readings after a period of continuous treatment, although this is not striking.

In summarizing the effects of treatment on seventy-two patients with rest or retropathic pain, pain of ischemic neuritis, and pain caused by ulceration and gangrene, it was found that twenty-four, or 33.3 per cent, secured persistent, good results (relief of pain and healing of the gangrenous lesions). These patients were treated by means of the bed only. Persistent, good results also were obtained in eighteen other cases, although in these cases other types of treatment were given simultaneously and may have been responsible for the improvement. No persistent benefit was obtained in thirty, or 41.7 per cent, of the seventy-two cases, regardless of whether the bed was used alone or in conjunction with other types of treatment. It has been our experience that treatment with the bed has given better results than treatment with pressure and suction or with intermittent venous compression. The advantages of the bed appear to be that the treatment can be continued over long periods of time without interruption, and that it can be combined with various vasodilating procedures without the use of any constriction or pressure to the legs and without effort on the part of the patient. We have found it necessary to vary the position of the bed and time of the cycle to adapt it to the individual patient. We have seen only one untoward result during treatment; the patient had a severe infection of the foot, associated with extensive gangrene, as the result of thromboangiitis obliterans. In this case, ascending lymphangitis and lymphadenitis developed. There is some question whether the treatment with the bed was in any way responsible for this.

In conclusion, I wish to say that, in my opinion, the oscillating bed is a definite contribution to the treatment of peripheral vascular disease. I do not believe that this treatment should supplant other methods of therapy, but, in many cases, particularly in the presence of severe pain which is difficult to control, it is a valuable addition to other types of therapy.

Discussion of the papers, "A Review of Success and Failure in the Treatment of Vasospasm by Sympathectomy," by Dr. Alfred W. Adson and Dr. Bayard T. Horton, Rochester, Minn., and "Immediate Effects and Late Results of Sympathetic Denervation of the Upper Extremity by Pre-Ganglionic Section," by Dr. Reginald H. Smithwick, Boston, Mass.

Dr. Ashley Oughterson, New Haven, Conn.—It is very stimulating to hear reports from these two clinics, the Massachusetts General Hospital and the Mayo Clinic, in which so much has been done to forward the study of vascular disease.

The experience of Dr. Adson, Dr. Smithwick, and others demonstrates that sympathetic denervation is effective when indicated.

I am afraid that anything I might add to the discussion of the operation on the upper extremity would add more confusion. We tried at first to make the operation as complete as possible, but some of the patients whose upper extremities had been operated on had a return of symptoms. After learning of the work of Dr. White and Dr. Smithwick, of the Boston group, we tried their operation, but we have not been able to make it uniformly successful, although it is better than the old procedure. This may have been due to differences in technique.

The syndrome of Raynaud's disease varies greatly; in some of the cases there is a pronounced emotional factor, whereas in others the symptoms are brought on by cold. Both factors may be present. It is our impression that in cases in which the emotional element is prominent we have had much more difficulty in getting a satisfactory result. We have seen that vasospasm may have a number of causes. It may be affected by a humoral mechanism or by the sympathetic nerves. As I have mentioned, there is evidence that Raynaud's syndrome frequently involves both. I think that in the future the work will probably evolve in such a manner as to indicate which of the operations may be eventually most effective.

I should prefer to say a few words about the general aspects of sympathectomy. As Dr. Adson has pointed out, it has now been in use more than fifteen years. When the operation was first introduced there were great hopes that it would be effective in relieving many symptoms of vascular disease. Those hopes, to some extent, have been fulfilled.

Sympathectomy is an operation of election, and, as is common with all operations of election, it should involve no risk to the patient and should leave the patient with no undesirable sequelae. The retroperitoneal approach for lumbar sympathectomy has made this operation relatively simple, and has eliminated the risk of the transperitoneal abdominal operation. Sympathetic denervation of the upper extremity was formerly followed by Horner's syndrome. As Dr. Adson pointed out, that is not necessary, even though we carry out an extensive operation in contradistinction to the one which seems indicated by the work of White and Smithwick. Thus, in the upper extremity, likewise, there are few undesirable sequelae.

The simplicity of the operation on the lower extremity, as contrasted with the upper, is considerable. This has encouraged us to use the operation more often on the lower extremities than we did formerly, that is, in more and more cases in which there was organic vascular occlusion, but in which a definite vasospastic element could also be demonstrated. Even though the blood flow may not be greatly increased, sympathectomy has the advantage that the effect is constant. Sympathectomy is also a most effective means of increasing the blood flow in a paralyzed limb. This has been sometimes overlooked, because we find orthopedic surgeons still trying to shorten the normal limb in cases of poliomyelitis. Children who have cold, sweaty extremities in which the circulation has not developed because of lack of muscular development may have their extremities lengthened if the operation is done before the epiphyses have united.

Histologic study has not demonstrated that the sympathetic nerves or ganglia are involved in any vasospastic phenomenon. Sympathectomy is therefore not directed at the etiology of the disease, and it is to be hoped that future investigation may provide a more rational treatment of such conditions as Raynaud's syndrome. However, it is well demonstrated, in the meantime, that sympathetic denervation has established itself as an effective therapeutic procedure over the period of fifteen years during which it has been used and has fulfilled the criteria of an elective operation.

Dr. Norman E. Freeman, Philadelphia, Pa.—Failures in the attempt to relieve vasospasm by sympathectomy have been associated with two processes which constitute real, major problems. One is that of sensitization by denervation. By this we mean that smooth muscle which has been robbed of its natural innervation becomes more sensitive to circulating hormones. Sensitization is much more effective after the postganglionic section which Dr. Adson and Dr. Smithwick have described.

The operations suggested by Dr. Smithwick and Dr. White, and described by Dr. Adson, have done much to avoid postganglionic denervation.

We are now confronted with the second major obstacle to successful surgical treatment, and that is regeneration. Whether it is regeneration, or whether it is the taking over of function by pathways which were already present, though dormant, may be a question in certain cases. Probably the latter will occur after incomplete operation, with recurrence of symptoms shortly after sympathectomy. The former is indicated by recurrence some months after the operation. Just how regeneration occurs is difficult to say. Preganglionic fibers will grow through muscle. They will grow through long stretches of tissue. If the ganglia are removed, it is difficult to see how the preganglionic fibers can come into contact with the heart muscle except through the agency of postganglionic neurons. Yet all of the postganglionic neurons have been removed by resection of the paravertebral ganglia. In spite of all this, inside of three or four months we have definite evidence of the resumption of control, sympathetic control, over the heart, in the experimental animal.

I think the problem of regeneration of sympathetic fibers is a major one, and not until we understand this fully can successful surgical treatment be assured.

Dr. Adson (closing).—I never take part in a controversial subject without being reminded of that play known as *Abie's Irish Rose*. After the couple was married, the priest and the rabbi concluded that there really was no material difference in their religion, since their respective groups expected to reach Heaven, although by different routes.

Discussions of this sort are extremely valuable, since they emphasize various phases of the subject. Although my views concerning the operative technique of sympathectomy for Raynaud's disease differ from those of Dr. Smithwick, I do want to emphasize the fact that such opinions are the result of observations, not of any personal animosity.

In the first place, we all agree that extensive lumbar ganglionectomy, whether done by the Royal, Pearl, Diaz, or the transperitoneal technique, results in dilatation of the peripheral vessels of the lower extremities. Though some hold that the vasodilating effect is caused by a preganglionic section of the sympathetic nerves, I am still of the opinion that the result is due to a thorough section of vasomotor fibers, whether the section is preganglionic or postganglionic. Removal of the fourth lumbar sympathetic ganglion, together with the first and second lumbar ganglia and the intervening trunk, is a combination of preganglionic and postganglionic section of the vasomotor fibers supplying the peripheral blood vessels of the lower extremities. Diaz's results were equally as good as those we have

obtained by resection of the second, third, and fourth lumbar ganglia and intervening trunk, although his procedure included the first and second sacral sympathetic ganglia, as well as the lumbar ganglia that we included. His procedure would naturally have to be considered as postganglionic section of the sympathetic fibers.

In reviewing the results we obtained by employing the Smithwick technique in the treatment of Raynaud's disease of the hands, we observed that changes in color would take place on exposing the hands to low temperatures. This, we think, was the result of leaving the vasomotor fibers intact, the explanation of which we believe is the fact that certain vasomotor fibers pass from the first thoracic nerve through the stellate ganglion to the brachial plexus. We further question the conception that the effectiveness of trunk resection of the third thoracic ganglion and division of the rami of the first and second thoracic nerve is greater than that of thorough resection of the lower cervical and first thoracic sympathetic ganglia, with removal of the sympathetic trunk in connection with ramisectomy of the eighth cervical and first thoracic nerves, a procedure which interrupts all sympathetic fibers that may enter the brachial plexus from lower thoracic ganglia. Many of our patients have had no recurrent symptoms during intervals of ten years. The work of Allen, Fathering, and Adson on sensitivity to epinephrine showed that although there was an increase in sensitivity to this drug following sympathectomy, there was no material difference in the reaction depending on whether the patient had been operated on by the Smithwick or Adson technique.

There is a possibility, as Freeman has stated, that regeneration may take place. However, the results of my study of experimental nerve regeneration indicated that if a gap of 2 cm. were permitted to exist between the severed ends of nerve fibers regeneration would rarely take place. This suggests that recurrences are more likely referable to the action of vasomotor fibers that have been overlooked at the time of operation. These fibers may have been injured sufficiently during the operation to account for their temporary dysfunction, but, as function became re-established, recurrent symptoms appeared.

Diseases resulting from spasm of the peripheral arteries of the fingers and hand occur sufficiently often to warrant further investigation, and it is my hope that some simple procedure may be developed to relieve the symptoms of this spasm. You may all be assured that I will employ the procedure if it is effective, regardless of who devised it.

Department of Reviews and Abstracts

Selected Abstracts

Thiele, G.: The Reactivity of Blood Pressure to Adrenaline in the First Years of Life. *Ztschr. f. Kreislaufforsch.* 31: 137, 1939.

This study was carried out on thirty-five young dogs. The blood pressure rise with maximum doses of adrenalin is slight at birth, and increases rapidly to reach adult magnitude at four months.

KATZ.

Osterwald, H.: The Action of Strophanthin in Experimental Coronary Insufficiency. *Ztschr. f. Kreislaufforsch.* 31: 225, 1939.

Eleven anesthetized dogs were used, and the flow in the left descending coronary artery was determined as well as that of the left pulmonary artery of left pulmonary vein by means of Rein stromuhrs, together with arterial and venous blood pressure.

He found that the coronary insufficiency produced by pituitrin, chloroform, or by ligation of the left descending coronary artery was improved by strophanthin, in that pulmonary flow and coronary flow increased.

KATZ.

Mönks, L.: Experimental Studies of Tonogenic Cardiac Dilatation Following Increased Venous Return. *Ztschr. f. Kreislaufforsch.* 31: 191, 1939.

Ten surviving rabbits' hearts were used, and it was found that infusion of saline into superior vena cava caused dilations of right auricle, elongation of right ventricle and rotation of heart on its long axis toward the left. Infusion into the pulmonary vein had its primary effect on the left auricle and ventricle with rotation to the right.

When a patent foramen ovale was present, both chambers were found to share the dilatation regardless of where the infusion was made.

These volume changes were reversible.

KATZ.

Gilligan, D. Rourke, Altschule, Mark D., and Linenthal, Arthur J.: Effects on the Cardiovascular System of Man of Fluids Administered Intravenously. *Arch. Int. Med.* 64: 505, 1939.

The effect of the intravenous administration of 1,000 to 1,500 c.c. of physiologic solution of sodium chloride on the glomerular filtration rate, as measured relatively by the urea clearance, of adults with normal renal and cardiovascular functions, has been studied. The fluids were injected at rates sufficiently rapid to cause increases in blood volume and cardiac output, decreases in plasma protein concentration, transitory increases in venous pressure and evidences of peripheral vasodilatation.

The glomerular filtration rate was not changed by the injections of fluid, even in those cases in which great changes in the systemic circulation were shown.

The absence of increase in glomerular filtration in the presence of hypervolemia, increased cardiac output, and lowered protein osmotic pressure, as induced in our studies, appears to result from specific adjustments in the renal vascular dynamics. No information is available from our studies as to the nature of such renal adjustments.

These results, together with those obtained by other investigators in certain clinical conditions and after the administration of certain drugs, demonstrate that the rate of glomerular filtration may not be affected in the presence of large changes in the systemic circulation.

AUTHORS.

Ogden, Eric, and Shock, N. W.: Voluntary Hypercirculation. *Am. J. M. Sc.* 198: 329, 1939.

Two subjects are discussed; both of them are able voluntarily to accelerate their pulse rates at the word of command. This acceleration is accompanied by increased systolic and diastolic blood pressures, increased rate of respiration, ventilation volume, oxygen intake, and carbon dioxide output. The onset and disappearance are abrupt.

The quantitative consideration of the magnitude and time relations of these functions indicates that there is a true hyperventilation with excess elimination of carbon dioxide, a true increase in metabolism with excess oxygen utilization, and a hypercirculation, or circulation in excess of the metabolic requirement. Epinephrine might be responsible for the cardiac acceleration and the increased blood pressure, and, by discharge of blood reservoirs, for the increased circulation. But it is believed that the phenomenon appears and disappears so rapidly that epinephrine cannot be solely held to account. In the nine reports cited, covering some fifteen other cases of voluntary acceleration of the heart, there is no instance in which the acceleration was not accompanied by one or more of the other phenomena described.

AUTHORS.

Schleicher, I.: Acute Cardiac Damage in Healthy Individuals Following Athletics. *Ztschr. f. Kreislaufforsch.* 31: 105, 1939.

Athletics can lead to cardiac damage in healthy subjects by causing trauma and commotio cordis, if excessive bodily exertion of long duration or of short, intense nature is carried out.

Following such heart damage death may occur, or myocardial infarction, chronic heart weakness, traumatic valvular defects, arrhythmias, and tachycardias may ensue. It would appear that infection, including focal infection and the so-called vagotonic disposition, may be considered a predisposing cause for the hazards.

Illustrative case reports are given, one of nonpenetrating chest wounds, six of long duration exertion, and two of severe exertion.

KATZ.

Schlomka, G., and Witsch, F.: The Evaluation of the Relative Duration of Systole. IV. In Obese People. *Ztschr. f. Kreislaufforsch.* 31: 142, 1939.

The electrical systole is on the average relatively longer in obese than normals of the same age group. This is based on measurements on 200 obese people. This increase in systole seems related to the degree of left axis shift.

KATZ.

Roemheld, L.: Alterations of Cardiac Minute Volume by Diet. *Ztschr. f. Kreislaufforsch.* 31: 73, 1939.

The author studied twenty patients and used Grollman's method for cardiac output. Normal persons and mild cardiacs showed an increase in cardiac minute output when the diet is increased by adding 1 to 1¼ liters of water or 6 to 10 grams sodium chloride daily to the regular diet. When the diet consists only of fruit or of salt-poor dry food, the minute volume output is decreased. Severe cardiacs, however, reacted in the exact reverse manner.

KATZ.

Evans, Courtenay: Changes in the Chest Lead Electrocardiogram in Coronary Thrombosis. *Brit. Heart J.* 1: 161, 1939.

In the T_1 type of electrocardiogram after coronary thrombosis, the changes in Lead IV occur in the following sequence. The initial wave R disappears immediately in half the cases, and elevation of the R-T segment, 3 mm. above the iso-electric level, occurs at the same time in three-quarters of the cases. The T wave becomes inverted on the third or fourth day, synchronous with or slightly earlier than inversion of T_1 , and sometimes many days earlier. At the same time, the R-T elevation diminishes, and, in half the cases, changes any time after the fourth day into a humped upward convexity with broad slurring of the curved portion. Return of RS-T to normal, with disappearance of the humping, occurs after several weeks. T-wave inversion disappears in half the cases between the third and sixth month, but in half the cases it persists. The initial wave R, when once absent, usually tends to remain absent; the initial complex in these cases sometimes becomes diphasic (QR).

In the T_2 type of electrocardiogram, RS-T is depressed 3 mm. below the iso-electric level, returning to normal within a few days in two-thirds of the cases. The initial R wave is present, the S wave is often small, and sometimes a W-shaped complex is seen. Later, humping of the S-T segment with a downward convexity occurs in a few cases, but is not common. The T wave is upright and tends to increase in amplitude; it may attain 13 to 19 mm. in the second or third week. As a rule the changes in Lead IV, after the initial RS-T depression has passed, are slight and not very helpful in diagnosis.

Post-mortem evidence suggests that T_1 and T_4 inversion, and absent R_4 with elevation of RS-T in Leads I, II, and IV, indicate an anterior infarction, and that T_2 and T_3 inversion with depression of R- T_4 indicates a posterior infarct. Where absence of R_4 and T_4 inversion is associated with inversion of T_2 and T_3 , the evidence points to infarction of both anterior and posterior ventricular walls. The third type of occlusion, involving the left circumflex artery and causing left lateral infarction, shows RS-T depression in Leads I, II, and IV, with inversion of T in Leads I, II, and IV. These changes are often of a transitory nature and may be associated with auricular fibrillation.

AUTHOR.

Eliaser, Maurice, Jr., and Konigsberg, Jerome: Electrocardiographic Findings in Cases of Ventricular Aneurysm. *Arch. Int. Med.* 64: 493, 1939.

There is an electrocardiographic syndrome, occurring in 27.3 per cent of cases of aneurysm of the left ventricle following occlusion of the coronary artery, which may be considered to be a presumptive sign of this lesion. It consists of a downward directed major deflection in Lead I, with inversion of the T wave and an upright P wave. The ventricular complex in Lead III is upright.

Another type, occurring in 36.4 per cent of cases, presents ventricular complexes directed downward in Leads II and III with an upright major deflection in Lead I that may or may not be of low amplitude.

In 18.2 per cent of cases of cardiac aneurysm, the electrocardiogram shows left bundle branch block, and there were a like number of various other equivocal records, which, although consistent with disease of the coronary artery, were not of diagnostic significance.

Roentgen examination, especially roentgenkymography, would seem to be the most reliable means of corroboration of the diagnosis of ventricular aneurysm and should be performed when one or the other of the two types of cardiogram observed in 63.7 per cent of all cases is obtained.

No correlation between the location of the aneurysm and the specific type of electrocardiogram obtained has been established.

The use of the Einthoven equilateral triangle is a convenient means of visualizing deviation of the axis. However, other more recent theories must be considered in order to explain the two divergent types of cardiogram obtained with pathologically identical lesions.

AUTHORS.

Radványi, Géza: *Electrocardiographic Prognosis.* Ztschr. f. Kreislau fforsch. 31: 83, 1939.

The author analyzed a follow-up study on forty-nine cases with intraventricular block or inverted T_1 or T_2 , and found that the outlook is not as serious as formerly thought. It is not the electrocardiogram but the underlying disease that determines the prognosis.

KATZ.

Graf, L.: *The Electrocardiogram in Single and Double Ovum Twins.* Ztschr. f. Kreislau fforsch. 31: 337, 1939.

There is a much greater similarity in electrocardiograms in single ovum twins than in double ovum twins. Cases of mirror image QRS complexes are described in the former type of twins. The study is based on twenty-four of the first, and fourteen of the second type of twins.

KATZ.

Schlomka, G., and Cramer, H.: *Sinus Arrhythmia in Presence of Extrasystoles.* Ztschr. f. Kreislau fforsch. 31: 240, 1939.

It was found that in the presence of extrasystoles, sinus arrhythmia was more noticeable than in their absence.

KATZ.

Marx, L.: *The Q-T Interval Following Extrasystoles.* Ztschr. f. Kreislau fforsch. 31: 42, 1939.

The author analyzed fifty instances of postextrasystolic beats and found that the Q-T interval was shorter than anticipated from Fridericia's formula relating electrical systole to cycle length, and this relative shortening was greater, the greater the compensatory pause. The author interprets this to indicate that large stroke volumes are the cause of this abbreviation of systoles.

KATZ.

Schlomka, G., and Dressen, M.: Physiological Irregularities of the Heart Beat. XI. Respiratory Variations of Q_s . Ztschr. f. Kreislaufforsch. 31: 46, 1939.

Respiratory variations in Q_s occur in normal subjects as well as in cardiaes. Usually this consists of an inspiratory decrease, occasionally an inspiratory increase in the size of the wave. The decrease in Q_s with inspiration seems most marked in those cases with the most marked sinus arrhythmia.

KATZ.

Spang, K., and Korth, C.: The Electrocardiogram in Hyperthyroidism. Arch. f. Kreislaufforsch. 4: 189, 1939.

This is a monograph of about 130 pages in which the literature has been thoroughly studied. The author discusses arrhythmias, contour, and the effect of medication. This study includes two hundred cases of their own. While all sorts of changes are seen, the authors emphasize the development of a depressed S-T and an inversion of the T wave as evidence of acute increase in the thyrotoxic state. They also point out frequency of tall P_2 and consider this evidence of stasis in the lesser circuit since as condition improves, P gets smaller and the curve shows a shift to the left.

Digitalis has little effect on heart rate in thyrotoxicosis, but an exaggerated ability to produce the digitalis T wave. This is considered of value diagnostically. Other details must be sought for in the original article.

KATZ.

Manning, G. W., McEarchern, C. G., and Hall, G. E.: Reflex Coronary Artery Spasm Following Sudden Occlusion of Other Coronary Branches. Arch. Int. Med. 64: 661, 1939.

The mortality following sudden occlusion of the anterior descending branch of the left coronary artery in the anesthetized dog is less than 10 per cent. For the conscious dog the mortality is about 40 per cent.

For sudden occlusion of the left circumflex branch, the mortality is about 25 per cent with anesthesia and about 75 per cent without.

The great increase in mortality for the conscious animal may be the result of a reflex spasm of collateral arterioles and small arteries producing additional areas of ischemia.

All the animals that died suddenly after ligation in the conscious state showed evidence of ventricular extrasystoles, tachycardia, and fibrillation in that sequence.

AUTHORS.

Master, A. M., Dack, Simon, and Jaffe, H. L.: Age, Sex, and Hypertension in Myocardial Infarction Due to Coronary Occlusion. Arch. Int. Med. 64: 767, 1939.

The influence of age, sex, and hypertension on the incidence, clinical course, and prognosis of coronary occlusion has been analyzed in 500 consecutive cases.

Approximately two-thirds of the attacks occurred between the ages of 45 and 65, and almost one-third before 50 years. The peak occurred in the sixth decade.

The number of initial attacks rose progressively until the age of 45 years; then a level was maintained until the age of 64, after which there was a rapid decrease. However, when the number of attacks was correlated with the census

of the general population in each age group, there was a progressive rise in the incidence of attacks with advancing age to 74 years.

Particular attention was paid to a group of 39 patients aged 27 to 39 years. The susceptibility of these young persons to coronary sclerosis and occlusion could not be attributed to rheumatic fever, syphilis, diabetes, hypertension, or a familial or hereditary trait.

The mortality rate varied with age, increasing gradually until the age of 59 and rising sharply in the older age groups. Coronary occlusion is rarely fatal before the age of 40, since the occlusive process is often localized to one artery and the myocardium is not diffusely damaged.

The frequency of multiple attacks was the same in all age groups. Young and old persons are equally susceptible to subsequent attacks of coronary occlusion after an initial attack.

The commonest cause of death before the age of 50 was arterial embolism; after 50, it was cardiac failure.

The ratio of men to women was only 3.4:1. The average age of the women was higher than that of the men, and the incidence in women below the age of 40 was relatively small.

Diabetes was frequent in women over 50 but uncommon in men below 70. In women the incidence rose sharply with increasing age.

Cardiac enlargement and heart failure increased with age, being uncommon in the young. They were more common in women than in men. Pulmonary edema with little or no pain not infrequently initiated an attack, particularly in women.

Hypertension occurred in more than half the men and in four-fifths of the women. The incidence rose with age from 36 per cent in the fourth decade to 74 per cent in the seventh decade. There was no effect on the mortality rate.

Hypertension is an etiological factor in coronary occlusion, for its incidence in this series was definitely greater than that calculated for the general population. Furthermore, the ratio of attacks per unit of the hypertensive male population was five to eight times as great as that for patients with normal blood pressure, although both ratios increased with age in the same proportion. Hypertension accelerates the aging process.

AUTHORS.

Maitra, J. M.: Coronary Occlusion. Medical Bureau 3: 185, 1938.

Notes from numerous cases of coronary thrombosis in native Indians are given, describing symptom of the sudden death, together with physical signs and electrocardiographic findings.

The author has found that in cases with chronic coronary occlusion with standard characteristics in electrocardiogram, the symptoms of external pain and discomfort may disappear completely after the use of hydrocyanic acid. He believes that fresh blood vessels develop throughout the myocardium and eventually form anastomoses. Several cases showing favorable results are recorded. There is a discussion of the anatomical explanation of symptoms and signs of coronary insufficiency.

McCULLOCH.

Müller, Carl: Angina Pectoris in Hereditary Xanthomatosis. Arch. Int. Med. 64: 675, 1939.

Hereditary heart disease due to xanthomatosis is fairly common. It is believed to have been demonstrated as a dominant factor in seventeen families. Xanthomatosis gives rise to a special form of arteriosclerosis which is etiologically and,

consequently, clinically different from ordinary arteriosclerosis. It is possible that it may be different anatomically, too. Xanthomatous deposits may cause valvular lesions, but far more commonly the changes are in the coronary arteries, with angina pectoris. This may occur in young but more frequently in middle-aged and old persons. Symptomatically this form of angina pectoris does not differ from the usual form. In addition to chronic and long-continued heart disease, the condition may cause sudden death. Infarction of the myocardium is also a frequent result. Hypercholesteremia is present, most marked in connection with xanthoma tuberosum, but there is no definite relation between hypercholesteremia and xanthomatous deposits in the skin. Xanthomatous cardiac lesions probably may develop in persons who have no evidence of xanthomatosis in the skin. Xanthoma tuberosum and xanthelasma may be overlooked in clinical examinations and may be confused with other cutaneous conditions also. The occurrence of heart disease in families should direct the attention to xanthomatosis, especially when rheumatic fever, syphilis, or hypertension does not appear to play any role. In the cases here reported, hypertension was infrequent. Finally, it seems possible that causal and prophylactic treatment may prove to be of value.

AUTHOR.

Middleton, William S., and Burke, Mead: *Streptococcus Viridans Endocarditis Lenta. A Clinico-Pathologic Analysis of the Experience in the Wisconsin General Hospital.* Am. J. M. Sc. 198: 301, 1939.

Certain details in this clinico-pathologic analysis of eighty-eight cases of *S. viridans* endocarditis lenta justify especial emphasis:

Further evidence is adduced to support the thesis of a close relationship between congenital and rheumatic lesions of the heart and endocarditis lenta.

Acute upper respiratory infections, rheumatic fever, infected abortion, dental extraction, and massage for nonspecific prostatitis apparently served as precipitating factors in the development of certain cases of this condition.

Contrary to the accepted opinion, congestive heart failure may attend or mask this condition.

The clinical manifestations and course of this affection are notoriously varied and inconstant. After the cardiac changes incident thereto, particular attention has been directed to its toxic and its embolic features. Splenic and renal changes, including embolism, were very frequent. Mycotic aneurysms offered serious diagnostic problems. Cerebral accidents were not infrequent. Occasionally a mycotic aneurysm of a cerebral vessel may explain certain neurologic phenomena of this condition. Again the clinical picture may suggest thyrotoxicosis, and the unexplained elevation of the basal metabolic rate may add to the diagnostic confusion.

This study offers material support to the importance of the diagnostic triad, i.e., petechiae, splenomegaly, and positive blood culture for the *S. viridans*. Given the background of a congenital or a rheumatic heart lesion and a remittent fever, this triad offers the logical direction of attack.

The prognosis of *S. viridans* endocarditis lenta is very grave. Only inferential evidence of the pace of the decline is offered by the circulatory, renal, embolic, toxic, constitutional, and hematologic reactions. Although remissions of varying durations and degrees are the rule, certain of these patients undergo a rapidly progressive decline. Attention has been directed to the ominous significance of the euphoria that attends late remissions.

This group included one instance of healed endocarditis lenta. The clinical activity apparently occurred at a period removed from the hospitalization. All therapy in the remaining number (87) was unavailing.

AUTHORS.

Crynes, S. F., and Hunter, Warren C.: Traumatic Rupture of the Pericardium. Arch. Int. Med. 64: 719, 1939.

Traumatic rupture of the pericardium is not, as the literature indicates, a rare occurrence. It is no doubt encountered as frequently in every series of autopsies on persons dying as a result of trauma as it has been in this series.

Commonly, pericardial rupture is merely one of many injuries and in most instances contributes little or nothing to the cause of death. One may rightly anticipate therefore that few examples of long survival will ever be recorded.

The pertinent data in 22 cases found among 4,107 consecutive and unselected cases studied at autopsy have been tabulated and evaluated. Among these, 1 case stands out conspicuously, not only in this group, but among all others on record, because of the fact that the child survived for two and one-half years, and, further, because of the singular mechanism responsible for the sudden death. This case is described in detail.

The views of others and the authors as to the mechanical principles involved in the production of pericardial rupture are given.

AUTHORS.

Harris, Jerome S., and Farber, Sidney: Transposition of the Great Cardiac Vessels, With Special Reference to the Phylogenetic Theory of Spitzer. Arch. Path. 28: 427, 1939.

In a review of the hypotheses concerning the pathogenesis of transposition of the great cardiac vessels, particular attention has been paid to the theories of Rokitansky and of Spitzer, since they represent the ontogenetic and phylogenetic aspects of this malformation. An attempt has been made to present in detail the essence of the theory of Spitzer as gathered from a study of all pertinent literature. Nineteen examples of transposition from the Infants' Hospital and the Children's Hospital collection have been analyzed in illustration of that theory. This series included examples of overriding aorta, complete transposition of the tricuspid valve, bulboventricular inversion, atresia of the tricuspid orifice, and cor biatriatum pseudotriloculare with mitral atresia. One case showed a very rare primitive arrangement of the chambers of the heart, while another showed the combination of fetal endocarditis and aortic transposition. Incidental malformations of the heart included various deformities of the interatrial and interventricular septums, valvular abnormalities, aortic coarctation, and a complete vascular circle around the trachea and esophagus.

In each case, particular attention was paid to the course of the main coronary arteries. Inversions, corrected transposition, and the relation of mitral atresia to transposition were briefly examined.

It may be concluded that the theory of Spitzer marks an important advance in the understanding of cardiac development and certain cardiac malformations. Although many data, accumulated from embryology, phylogeny, and teratology, tend to support the theory, further proof will be necessary before it can be accepted completely.

AUTHORS.

Robinson, Samuel C., and Brucer, Marshall: Range of Normal Blood Pressure: A Statistical and Clinical Study of 11,383 Persons. Arch. Int. Med. 64: 409, 1939.

A new and more rational range of normal blood pressure is postulated as the result of (1) a statistical study of 10,883 persons, (2) a study of five to ten year continuous records of 500 persons, and (3) an appraisal of mortality at

various pressure levels. The normal range of systolic blood pressure for men and women is from 90 to 120 mm. of mercury. The normal range of diastolic blood pressure for men and women is from 60 to 80 mm. of mercury. A normal person attains his mature blood pressure at about adolescence and keeps that range throughout life, except for a slight rise at about the twentieth year. Normal blood pressure does not rise with age. Prehypertensive and hypertensive pressures do rise with age.

"Hypotension" is neither a disease nor a disease entity; it is an ideal blood pressure level. In the absence of other findings this is true of pressures that occasionally dip to the level of 80 systolic and 50 diastolic. The commonly described symptoms of the disease called "hypotension" can be ascribed with equal statistical accuracy to any level of blood pressure.

Blood pressure should be considered a physiologic measurement in continual diurnal flux, highest during the afternoon, lowest during the early morning hours. The daily and yearly variation of normal blood pressure is from 5 to 10 mm. of mercury. Higher levels of blood pressure show proportionately greater and more erratic yearly variations. Lower levels of blood pressure show smaller and less erratic yearly variations. A blood pressure history is more nearly normal as it shows occasional pressures below 110 systolic and 70 diastolic. A person who has a history of pressures which occasionally dip to the 90 systolic and 60 diastolic level, or even to the upper part of the 80 to 90 systolic and 50 to 60 diastolic range, has an added assurance of not becoming hypertensive.

A blood pressure history of over 120 systolic and 80 diastolic over a ten year span in a man or woman is pathologic, and is an almost infallible sign of incipient hypertension. Once a pressure is definitely established in this range it seldom if ever will become normal. Transient elevations of blood pressure should not be ignored. They should be suspected of a further, more frequent, and possible permanent rise. Moderately high blood pressures are incipiently hypertensive. Persons with hypertensive heart disease are recruited from persons with incipiently hypertensive blood pressure levels. High blood pressures tend to become even higher, the higher pressures invariably resulting in hyperpiesia. High blood pressure is a long-term disease having its genesis at an early age. It is not a disease that suddenly emerges with middle age. Slightly more than 40 per cent of the adult population is either actually or incipiently hypertensive.

A study of any normal physiologic measurement must check with mortality data. One of the criteria for the selection of a normal range is that it be compatible with the lowest possible mortality and the longest life span. The mortality rate increases progressively with an increase in systolic or diastolic blood pressure. Persons with low blood pressures have the lowest mortality rate. Those with blood pressures persistently over 120 mm. of mercury systolic and 80 mm. diastolic have a higher mortality rate than those with blood pressures persistently under 120 mm. systolic and 80 mm. diastolic.

AUTHORS.

Rasmussen, Hakon, and Thingstad, Rolv: Cardiovascular Changes in Essential Hypertension With Special Reference to the Electrocardiogram in Hypertension. *Acta med. Scandinav.* 101: 237, 1939.

A group of 100 patients with essential hypertension has been examined with regard to cardiovascular changes (cardiac function, size of heart, electrocardiogram, breadth of aorta, calcareous deposits in aorta and in the tibial arteries), and the findings have been more closely analyzed.

Only 8 per cent of the patients were without any pathologic findings (of varying import) in the cardiovascular system.

The height of the blood pressure was found independent of the degree of cardiac enlargement and electrocardiographic changes.

A study of the relationship between electrocardiogram and heart size brought forward some important points with a bearing on the pathogenesis of the electrocardiogram in hypertension and on the pathogenesis of the so-called "bundle branch electrocardiogram of commoner form," and the following conclusions were drawn:

Electrocardiograms of hypertensive patients are without any constraint grouped into four distinct types, characterized by varying alterations in the QRS deflection, S-T segment and T wave. The types seem to represent different stages of one and the same evolution. A closer examination of the relation between these four electrocardiographic types and the cardiac enlargement revealed a strong correlation between these types and the size of the heart. Thus the Types 1 and 2 with comparatively small changes in the electrocardiogram corresponded to slight and moderate enlargement of the hearts, while the patients with gross changes in electrocardiogram, Type 3 ("left ventricular preponderance curve") and Type 4 ("bundle branch block electrocardiogram of commoner form"), had the larger hearts.

The authors feel, therefore, that the electrocardiographic changes, above described as characteristic of the electrocardiogram of hypertension, are due to varying degrees of left ventricular enlargement (dilatation and/or hypertrophy), and not due to disease of the coronary arteries.

The bundle branch block electrocardiogram of commoner type (our Type 4) was observed in 7 of our 100 hypertensive patients. An analysis of the 7 cases together with another group of 21 cases with this electrocardiographic picture revealed that all 28 cases with "bundle branch block electrocardiogram of commoner form" were characterized by gross left ventricular enlargement. The chief cause of "bundle branch block electrocardiogram of commoner form" (classical terminology: right bundle branch block) is supposed to be severe left ventricular enlargement.

AUTHORS.

Thomas, Henry M., Jr.: Transient Paralysis From Postural Hypotension. Bull. Johns Hopkins Hosp. 65: 329, 1939.

A case of recurring transient paralysis of the right arm and leg is reported. The attacks occurred when the patient was upright, and frequently soon after arising from a sitting or lying position. He was found to suffer from a moderate form of postural hypotension which, in conjunction with cerebral arteriosclerosis, offered an explanation for the mechanism of the attacks. When the patient was elevated on a mechanical tilting table the systolic blood pressure fell below 90 mm. of mercury and temporary paralysis of the right leg occurred. Most of the previously reported cases of recurrent transient paralysis of brief duration probably belong in the same group.

Momentary clouding of the vision in one eye occurred in some of the attacks and probably resulted from temporarily inadequate blood flow through the ophthalmic branch of the internal carotid artery of the central retinal artery.

Treatment designed to prevent excessive drops in blood pressure has greatly diminished the number and severity of the attacks.

AUTHOR.

Miller, H. R.: *The Occurrence of Coronary Artery Thrombosis in Polycythemia Vera*. *Am. J. M. Sc.* 198: 323, 1939.

Although there have been extensive investigations on the principles underlying the mechanism of blood clotting and on the formation and organization of thrombi, we are still unable to explain the precipitating cause of an intravascular clot. Nowhere is this truer than in connection with the coronary arteries, and this problem assumes a fresh interest in connection with an analysis of coronary thrombosis in polycythemia when these vessels remain unaltered. The cases we have described illustrate that the clinical manifestations of thrombosis in a normal coronary vessel are indistinguishable from those observed in thrombosis of arteriosclerotic coronaries. These clinical features range from complete silence, e.g., few or no clinical signs at the time of the occurrence of the thrombosis as in some of our cases, to sudden and dramatic onset of shock, pain, and so on, as observed in our last case. The sequelae of disturbed cardiovascular hemodynamics and the evolution of anatomic alterations in the heart are not different for polycythemic patients who develop coronary thrombosis. Arteriosclerosis was absent, or at most minimal, in the coronary tributaries; in several instances, this complete or almost complete freedom of coronary sclerosis was in contrast to the general arteriosclerosis of other parts of the vascular system. The myocardial lesions were not limited to microscopic size but were gross and followed the occlusion of good-sized coronary vessels. The five cases in this series of seven polycythemics examined at autopsy suggest that the concurrence of polycythemia vera with coronary thrombosis or with marked myocardial damage of the type associated with coronary thrombosis, is more frequent than we were wont to believe and that coronary thrombosis, as well as other arterial and venous thromboses, is not to be dissociated from the pathogenesis of polycythemia vera.

It is of some interest to direct attention to the clinical seizures of precordial pain in polycythemic individuals in whom the coronary vessels are not occluded. The character and the mechanism of this manifestation may be akin to that observed, with and without intermittent claudication, in states of anemia. It has long been known that polycythemia or anemia may be responsible for many of the same clinical features and among them, we have reason to believe, precordial pain should be included.

AUTHOR.

Katzin, Herbert M., Waller, John V., and Blumgart, Herrman L.: "Cardiac Cirrhosis" of the Liver. *Arch. Int. Med.* 64: 457, 1939.

An investigation of an unselected series of 2,000 consecutive cases in which autopsy was performed was undertaken in order to learn the incidence, types, and degrees of hepatic fibrosis in cases of congestive failure and to make a comparison of these findings with those in cases in which congestive failure was absent.

Of the 286 cases of chronic passive congestion, there was an increase of hepatic fibrous tissue in ninety-five, or 33 per cent. In 1,714 cases in which chronic passive congestion was absent the incidence of hepatic fibrosis was 12 per cent. The causal significance of chronic passive congestion in the production of hepatic fibrosis was emphasized by the increasing incidence and severity of the fibrosis with increasing duration of congestive heart failure. The incidence of each of the various kinds of fibrosis except biliary fibrosis was higher in 286 cases of congestive failure than in the remaining 1,714. The only type of increase in connective tissue peculiar to the cases of cardiac decompensation was central fibrosis, for, with a single exception, no instance of central fibrosis was found in 1,714 cases in which autopsy disclosed an absence of congestive failure. Of

particular interest was the finding of increased periportal connective tissue in 23 per cent of the 286 cases of congestive failure, as compared with an incidence of 9 per cent in the 1,714 cases in which chronic passive congestion was absent. This suggests that chronic passive congestion with resulting anoxemia, by increasing the susceptibility of the hepatic tissue, is also a contributing factor to fibrosis in the portal areas.

By the evidence obtained in this investigation the meaning of the term "cardiac cirrhosis" is clarified. Cardiac cirrhosis signifying morphologic increase in connective tissue in the liver consequent to congestive failure is present in the majority of patients who have suffered from even mild congestive failure for nine months or more; the fibrosis may be central or portal or both. Clinical cardiac cirrhosis, signifying extreme fibrosis which clearly results from chronic passive congestion and which causes evidences of portal obstruction, does occur, but is rare. Of the 286 cases of congestive failure, there were only fifteen in which marked but not necessarily predominant ascites required abdominal paracentesis. The clinical diagnosis of cardiac cirrhosis can be made only rarely, since it must be based on the finding of preponderant ascites, a small liver in spite of elevation of the venous pressure, and particularly the presence of a palpable spleen. Not infrequently, however, the liver may be enlarged. In such cases, although increased fibrous tissue is present and the surface of the liver is generally nontender and sometimes somewhat irregular, the dilatation of the sinusoids leads to an increase in the size of the liver. In a patient in whose case a clinical diagnosis of cardiac cirrhosis has been made, one may find portal or central fibrosis, singly or in combination, or diffuse patchy fibrosis.

AUTHORS.

Rabb, W., and Schönbrunner, E.: *The Tendency of the Electrocardiogram to Become Normal in Angina Pectoris Patients Whose Adrenals Have Been Irradiated.* Arch. f. Kreislaufforsch. 4: 362, 1939.

Twenty-eight out of thirty-eight patients with angina pectoris were subjectively improved following one or more deep x-ray irradiations of the adrenal areas and were free of symptoms thereafter for eleven months on the average.

In ten out of thirteen patients showing an electrocardiogram of hypoxia (either at rest or during exercise), there was a tendency for the electrocardiogram to return to normal. The authors attribute these changes to irradiation therapy.

KATZ.

Edens, E.: *Indirect and Direct Strophanthin Action.* Ztschr. f. Kreislaufforsch. 31: 177, 1939.

Extrasystoles resulting from indirect strophanthin action are no ground for stopping drug when the heart's condition requires its use.

KATZ.

Book Reviews

ANGINA PECTORIS: NERVE PATHWAYS, PHYSIOLOGY, SYMPTOMATOLOGY, AND TREATMENT. By Heyman R. Miller, M.D., Attending Physician, Sydenham Hospital, Associate Attending Physician, Montefiore Hospital, New York. Baltimore, 1939, 275 pages, 39 illustrations, \$3.25, The Williams and Wilkins Company.

This book contains chapters on the clinical features of anginal pain, the anatomic arrangement of the nerves which transmit it, and the physiologic and psychologic theories which have been evolved to explain the production of the attacks and the variable intensity of their reception in the sensorium. A quarter of the book is devoted to the medical and surgical treatment of the anginal syndrome.

The outstanding feature of the book is its series of anatomic drawings. These figures, prepared in collaboration with Dr. V. L. Lyons and drawn by Mrs. S. T. Johnson, show in progressive detail the complex network of sympathetic and vagal fibers which carry afferent impulses from the heart to the spinal cord. The drawings give an exceptionally clear, three-dimensional portrayal of the course of afferent fibers through the middle and inferior cardiac nerves to the corresponding cervical sympathetic ganglia, and their descent in the paravertebral sympathetic chains to the upper thoracic ganglia. Their central projection through the white rami communicantes and over the posterior spinal roots is equally well illustrated. This anatomic exposition is, however, open to one important criticism—the lack of emphasis on the role played by the thoracic cardiac nerves. The latter, which are so important in the neurosurgical treatment of angina pectoris, run directly across the posterior mediastinum to the upper ganglia of the thoracic sympathetic chain. These connections are included in some of the figures, but no functional significance is indicated in any. Their omission is particularly glaring in Figs. 11 and 12. Semi-diagrammatic drawings such as these should be self-explanatory, but it requires a careful perusal of the text to extract the fact that the thoracic cardiac nerves play an important role in pain transmission. In order to emphasize their importance, it is not necessary to do more than point out that before their discovery, a decade ago, cervical sympathectomy was in disrepute because it failed to relieve cardiac pain in at least a third of the patients submitted to operation.

As regards the chapter on surgical treatment, the text suffers somewhat from the fact that it includes no illustrative case histories, and no single surgical procedure is definitely favored. On the other hand, the discussion of medical treatment is unnecessarily detailed in a book like this, concerned, as it is, largely with the nervous pathways; an important omission among the details is the failure to point out the great value of digitalis, at times lifesaving when acute congestive failure complicates coronary thrombosis; coramine is given far too much credit.

The bibliography is comprehensive and for the most part satisfactory, but there are only two brief references to the extensive work of Leriche and no mention of O'Shaughnessy's new method of cardio-omentopexy.

In estimating the value of the book as a whole, it can be recommended highly for the technical clarity of its portrayal of the cardiac nerves, but the description of medical and surgical therapy adds little to that of previous publications.

JAMES C. WHITE

CARDIOVASCULAR DISEASES. THEIR DIAGNOSIS AND TREATMENT. By David Scherf, M.D., and Linn J. Boyd, M.D., Associate Professor of Clinical Medicine, and Professor of Medicine, respectively, The New York Medical College, Flower and Fifth Avenue Hospitals, New York. St. Louis, 1939, 431 pages, The C. V. Mosby Co.

Except for slight changes in the order of the chapters, this book is essentially a translation of the fourth edition of Scherf's "*Klinik und Therapie der Herzkrankheiten und der Gefässerkrankungen*," published in 1938, and reviewed in this JOURNAL (16: 260, 1938). There have been a few minor additions, of which the least valuable are in the section dealing with congenital defects.

As a series of disconnected lectures to postgraduate students, the volume of Scherf was of some interest in presenting the current viewpoint of the Viennese school on certain aspects of cardiology. As a monograph on the diagnosis and treatment of cardiac and peripheral vascular diseases it is inadequate, and inferior to a number of texts already available in English. Incidentally, the translation, in places, is far from smooth. For example, on page 373, occurs this sentence: "The supervision of properly executed digitalis therapy belongs among the most important therapeutic acts of the physician."

No bibliography is given; only the briefest reference is made to electrocardiography and roentgenologic examination; there are ten text figures. Etiologic classification is ignored, both in arrangement of material and discussion. It is a record of personal experience on selected topics. The clinical descriptions are concise and clear. There are specific recommendations with regard to therapy.

The book is intended chiefly to serve as a handy guide for the "busy practitioner," but it does not fill a gap in the literature of the subject, so that there was really no need for the translation.

ROBERT L. LEVY.

AKTUELLE KREISLAUFFRAGEN. 14. ÄRZTLICHER FORTBILDUNGSLEHRGANG IN BAD-NAUHEIM. By fourteen contributors. 1939, 169 pages, 81 illustrations, Theodor Steinkopff, Dresden and Leipzig.

This book contains fourteen papers given as postgraduate lectures at Bad Nauheim, Sept. 23 to 25, 1938, and deals with many subjects pertaining to the heart and circulation. In the order in which the papers appear, we have: (1) "Recent Advances in Hemodynamics," by Ph. Broemser. Observations are recorded on the pulse rate, blood volume, blood pressure, and peripheral resistance during exercise, with trained and untrained subjects. In the trained subject, the pulse rate changed very little with effort, whereas the blood volume and minute volume increased. The systolic blood pressure was slightly elevated and the diastolic decreased. The effect of adrenalin was much more rapid in the trained than in the untrained subject.

(2) "The Control of the Circulation," by Eb. Koch. This is a verbose and highly academic discussion of some well-known, as well as unknown, factors controlling the circulation to various parts of the body.

(3) "Clinical Problems of Pulmonary Circulation," by Max Hochrein, a discussion—not at all profound, and quite rambling—of the physiology of the pulmonary circulation, with an attempt to explain such clinical entities as pulmonary edema, pulmonary embolism, etc.

(4) "The Question of Heredity in Cardiovascular Pathology," by Wm. Weitz. The author considers that heredity plays a role in the etiology of the following: Congenital heart and vascular defects, such acquired heart lesions as rheumatic heart disease and coronary disease, cardiac neurosis, essential hypertension and hypotension, thromboangiitis obliterans, varices, and hemophilia.

(5) "Dilatation and Hypertrophy of the Heart," by Eugene Kirch. A sound discussion of the subject, both from the clinical and experimental standpoint. The term "myogenic dilatation" is used to denote cardiac dilatation resulting from degenerative changes in the myocardium, and "tonogenic dilatation," an increase in the heart cavity in the absence of myocardial disease.

(6) "The Treatment of the Irregular Heart," by Ernst Edens. Most attention is paid to the treatment of auricular fibrillation, but nothing new is advanced. The author is much impressed by the effects of strophanthin intravenously in cases of auricular fibrillation with rapid ventricular rate and congestive failure. He advises strophanthin instead of digitalis in chronic fibrillation with slow ventricular rate and congestive failure. Paroxysmal auricular fibrillation is treated with strophanthin during and after the attack. Similarly, in cases of auricular flutter, the author states that strophanthin is more useful than digitalis or quinidine, a statement which many American clinicians will question. Ventricular extrasystoles occurring in damaged hearts are treated with strophanthin.

(7) "The Rôle of the Circulation in Surgery," by E. Rehn. A mediocre discussion dealing chiefly with postoperative shock and containing nothing new.

(8) "Operative Indications in Circulatory Diseases," by H. Bohnenkamp. The indications for operations in adhesive pericarditis are presented. A discussion is given of the treatment of angina pectoris by sympathectomy and total thyroidectomy, two procedures now largely abandoned in America. Some attention is paid to nerve section and injection of veins in the management of peripheral vascular disease, but nothing new is advanced.

(9) "Circulatory Questions in Pediatrics," by W. Keller. The author speaks of childhood vasoneurosis, under which he includes the changes in the circulation that occur when the body is brought from the horizontal to the upright position.

(10) "Effect of Emotional Influences on the Course of Circulatory Disorders," by V. Weizsäcker. A very general discussion of the influence of emotional and psychic factors on the clinical manifestations of cardiovascular disease.

(11) "The Influence of Respiration on the Intrathoracic Veins and Lymphatics," by W. Pfuhl. The author takes several pages to explain the well-known aspirating effect of the negative pressure in the thorax on the return circulation to the heart.

(12) "New Roentgen Results," by W. Böhme. The author relates his observations on the blood flow through the heart made with the roentgenkinematograph, and emphasizes the value of the method in the study of circulatory problems.

(13) "The Importance of Recording the Heart Sounds," by A. Weber. A method for the optical registration of the heart sounds is presented, but the author overestimates the diagnostic value of heart sound records.

(14) "The Dietetic Treatment of Cardiac Patients," by H. Eppinger. In spite of the title, the author pays little attention to the diet, but confines his remarks to the treatment of cardiac edema with drugs. For congestive failure, he advises a diet rich in potassium and poor in sodium chloride.

Apparently compiled for the practitioner, as suggested by the title, this book, with the exception of the paper by Edens on "The Treatment of Cardiac Irregularities," contains little material of practical importance to the practitioner of medicine. The theoretical discussions of the various subjects are at times verbose and contain nothing new.

R. W. SCOTT.

SYMPOSIUM ON THE SYNAPSE: By Herbert S. Gasser, Joseph Erlanger, Detlev W. Bronk, Rafael Lorente de Nó, and Alexander Forbes. 111 pages, 57 illustrations, \$2.00, Charles C. Thomas, Springfield and Baltimore, 1939.

This is a symposium on the mechanisms of nervous transmission across synapses by the American scientists best qualified to discuss the subject. The papers were

first given before the American Physiological Society, at Toronto, in April, 1939, and later published in the *Journal of Neurophysiology*. This volume is a reprint.

The material given is the "last word" on its subject. It concerns students of the heart and circulation only because these organs contain, and are influenced by, nervous mechanisms presumably of the character here described.

ISAAC STARR.

THE PATIENT AS A PERSON: By G. Canby Robinson, M.D., LL.D., Sc.D., Lecturer in Medicine, Johns Hopkins University. The Commonwealth Fund, 1939, 440 pages, \$3.00. London, Humphrey Milford, Oxford University Press.

The discovery, which Dr. Robinson makes in this book, that the hospital patient has a life apart from that in the ward, discloses a certain amount of naïveté. It is similar to the recent discovery which the psychoanalysts have made, namely, that their patients possess a body as well as a conscious and unconscious mind, psychosomatic medicine. However, both discoveries possess this in common—that while the social components of disease, on the one hand, and the physiologic components of emotion, on the other, have been recognized since the time of Hippocrates, and before, nothing much has been done about it. These problems have been stated but not answered. Dr. Robinson proposes to do something about it.

In this very readable book, he gives the results of a careful social study of 174 patients from the dispensary and wards of the Johns Hopkins Hospital. The title is intriguing, the material interesting and well presented. While the subject is not new, especially to the physician in general practice, who daily appraises the personality and social problems of his patients in their own home and family setting, the emphasis on it is stimulating and refreshing. It should have a particular appeal to younger medical students and their full-time academic instructors. The methods used in this study are admirable, paralleling the careful collection and analysis of data in any thoughtfully planned clinical investigation. It is an important contribution to the understanding and control of social adversity.

The 174 patients are classified in various disease categories: those with circulatory, respiratory, and digestive symptoms, respectively; the diabetic, the nephritic, the epileptic, etc. "The book is based upon information obtained directly from individual patients from their own accounts of the circumstances of their lives and from observing them in the hospital and in their homes." Dr. Robinson "made nearly all of the initial interviews and home visits himself." He found "personal inadequacy" as the one basic adverse condition in most of his patients. "Negro patients showed much less severe reactions to adversity as evidenced by worry, anxiety, and emotional strain."

In the patient with circulatory symptoms, Dr. Robinson believes that the "basic problem presented . . . is the adjustment of his life to his physical limitations, so that he may live constantly within these limitations and at the same time achieve a maximum of usefulness, efficiency, and happiness as a member of his social group." In the case of these patients with cardiovascular disease, he concludes: "It is clear that consideration of social and emotional disturbances, while by no means replacing rest, physical hygiene, and the judicious use of digitalis and other drugs, should constantly take an equal place beside them."

The patients with respiratory symptoms disclose other interesting, somewhat specific reactions: "The effect on respiration of the major emotions of fear, anger, disgust, wonder, and pleasure is a matter of common knowledge, but less

is known about the relation of more prolonged forms of emotional strain to abnormal respiratory action, such as coughing, rapid and shallow breathing, and sighing."

Of patients with digestive symptoms, he writes: "It may be said, however, that they show quite clearly the relationship of emotional disturbances to digestive symptoms both when organic disease is present and when no evidence of it is found."

In the final chapter on the treatment of the patient as a whole, Dr. Robinson concludes that in the teaching hospitals throughout this country a department covering the social aspects of illness should be established, similar to that recently developed in the University of Brussels, under the direction of Professor René Sand.

This book can be heartily recommended to those interested in the social background and emotional factors of disease. The material collected and presented by a physician has a slightly different flavor than that of similar studies made by trained social workers ("The Social Component in Medical Care," by Janet Thornton and Marjorie Knauth). In considering the patient as a person, in addition to the emphasis on social adversity, one might wish for more data on his "personal inadequacy"—his emotional life, his conscious and unconscious drives, his childhood and adult patterns of conduct, his conflicts and frustrations, his total personality.

WALTER W. HAMBURGER.

Announcements

REVISED CARDIAC CLINIC DIRECTORY NOW READY FOR DISTRIBUTION

It is announced by the New York Tuberculosis and Health Association that a revised, up-to-the-minute directory of the city's affiliated cardiac clinics is just off the press and ready for general distribution. The directory, compiled by the Heart Committee of the Association, covers the entire city, lists all cardiac clinics affiliated with the New York Heart Association, notes the clinic chiefs and social workers connected with each hospital, and quotes the hours the various clinics are at the public's disposal. For the first time, it carries a list of employment services and rehabilitation bureaus available to those suffering from heart disease.

The directory is for the use of social workers, public health nurses, and teachers, and copies may be obtained free of charge at the offices of the New York Tuberculosis and Health Association, 386 Fourth Avenue, New York City.

REVISED EDITION OF STANDARD WORK ON HEART DISEASES JUST OFF PRESS

Far more comprehensive and containing twice as many pages as any of its predecessors, the revised Fourth Edition of the diagnostic criteria of the New York Heart Association, "Nomenclature and Criteria for Diagnosis of Diseases of the Heart," is just off the press. This book, known in previous editions as the "Criteria for the Classification and Diagnosis of Heart Disease," has long been regarded as the standard work of its kind both in this country and abroad, and its fundamental purpose is to develop a precise and scientific nomenclature for the diagnosis of heart disease. The first edition appeared in 1928.

This new edition dwarfs all its forerunners, including, as it does, an authoritative outline of the three closely related fields of electrocardiography, radiology, and pathology, in addition to all-important clinical material.

Of the new material that has not appeared in any earlier edition, probably the most important is the section titled "An Outline for the Pathological Diagnosis of Cardiovascular Diseases and Anomalies," comprising nine chapters, 100 pages, and 52 illustrations. It was developed by men who are recognized authorities in their field and represents several years of intensive work.

Another valuable new section—"Therapeutic Classification"—purposes to guide physicians, nurses, and others in regulating the physical activity of cardiac patients.

The text relating to the clinical classification and diagnosis of heart disease has been revised, and although all necessary descriptive titles, together with definitions and instructions for their proper use, have been retained, a great deal of new material has been added. Another innovation finds the functional disorders of the heart placed among the titles for the diagnosis of heart disease, agreeing with the Standard Classified Nomenclature of Disease.

Dr. Harold E. B. Pardee served as chairman of the committee which directed revision of the book, and his colleagues included Doctors Arthur C. DeGraff, Clarence E. de la Chapelle, Cary Eggleston, Charles E. Kossmann, Robert L. Levy, and John B. Schwedel.

Dr. de la Chapelle was chairman of the committee which contributed the section "An Outline for the Pathological Diagnosis of Cardiovascular Diseases and Anomalies." His associates were Doctors William C. Von Glahn, Irving Graef, Robert A. Moore, Douglas Symmers, B. Morgan Vance, and the late Louis Gross.

As has been the case in previous years, the New York Tuberculosis and Health Association has arranged to distribute the book through the American Heart Association, which has adopted the volume as its official text. Copies may be obtained from the American Heart Association, 50 West 50th Street, New York City, at \$2.00 per copy. A limited number of Spanish translations are also available.

Corrigendum

In the article, "Convallan in Cardiac Therapy," by Ralph H. Major, M.D., and Lee H. Leger, M.D., which appeared in the October number of the *Journal*, Figures 3 and 4 (p. 446) should be transposed in order to correspond with the legends.

American Heart Association, Inc.

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THE American Heart Association, sponsor of the first International Health Broadcast, stands alone as the national organization devoted to educational work relating to diseases of the heart. Its Board of Directors is composed of twenty-five physicians representing every portion of the country.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning circulation of blood and lymph. Any physician or investigator in good standing may become a member of the section after election to the American Heart Association and payment of dues to that organization.

To coordinate and distribute pertinent information, a central office is maintained, and from it issues an ever widening stream of books, pamphlets, charts, posters, films, and slides. These activities all concern the recognition, prevention or treatment of the leading cause of death in the United States, diseases of the heart. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The income from membership and donations provides the sole support of the Association. Lack of adequate funds seriously hampers more widespread educational and research work imperative at this time. Great progress has been made, but much remains to be done.

Annual membership is \$5.00 a year and journal membership at \$10.00 includes a year's subscription (January-December) to the AMERICAN HEART JOURNAL and annual membership in this Association. A cordial invitation to join in this crusade is extended to you.

The American Heart Association solicits your support to the end that it may continue more effectively the campaign to which it has devoted all its energy.

*Executive Committee.

The American Heart Journal

VOL. 18

DECEMBER, 1939

No. 6

Original Communications

THE SPEED OF HEALING OF MYOCARDIAL INFARCTION

A STUDY OF THE PATHOLOGIC ANATOMY IN SEVENTY-TWO CASES

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BOSTON, MASS.

AND

JORGE SALCEDO-SALGAR, M.D.
BOGOTA, COLOMBIA

INTRODUCTION

THE treatment of any pathologic process can be carried out intelligently and scientifically only when it is based on a thorough understanding not only of how the lesion develops, but also of the means by which it heals and the speed with which this healing takes place. It has been known for a long time that occlusion of a main coronary artery or of a large branch will produce an infarct in the myocardium. It is also a well-recognized fact that, if the patient continues to live, such an infarct will undergo a process of healing, consisting of removal of the necrotic muscle fibers and replacement of them by connective tissue which in time forms a firm, contracted, fibrous scar.

It is very difficult, however, to find in the literature any exact description of the details of this process and, particularly, any discussion of the speed with which healing may be expected to take place in the human heart. This study was therefore undertaken in the hope that conclusions could be drawn which would be of value in the treatment of myocardial infarcts.

LITERATURE

The literature on coronary thrombosis and myocardial infarction is very extensive and, therefore, practically impossible to review here in any detail. The process of healing has been studied both in human autopsy material and experimentally.

From the Mallory Institute of Pathology, Boston City Hospital, and the Massachusetts General Hospital.

Presented before the New England Heart Association, Massachusetts General Hospital Meeting, November, 1937.

Received for publication June 7, 1939.

It was not until 1880 that pathologists began to show any particular interest in myocardial infarcts and really to grasp their significance. Undoubtedly, isolated instances had been described before this time. In this year (1880). Weigert,¹ in a paper entitled "Ueber die pathologischen Gerinnungsvorgänge," showed that myocardial infarcts were analogous to infarcts occurring elsewhere in the body. He described both the gross and microscopic appearance of acute myocardial infarcts and said that the healing process consisted in the removal of the necrotic muscle and its replacement by granulation and, eventually, by scar tissue. He also knew that a fibrinous pericarditis and an endocardial thrombus were likely to occur and that these also might be transformed into scar tissue. In the same year, Ziegler² introduced the term *myomalacia cordis*, in referring to these lesions.

From this time on, as a result of further refinements in histologic technique, more details of the process were gradually learned, but very little attention seems to have been paid to the speed with which healing occurs. It was not until the publication of Levine's³ monograph on coronary thrombosis, in 1929, that there was any detailed attempt to correlate the age of the infarct with the gross and histologic findings. From the cases in his series in which an autopsy was performed, 46 in all, he drew the following conclusions: (1) Necrosis of muscle is the predominating feature from the fourth day to the end of the third week; (2) repair by connective tissue is demonstrable on the sixth or seventh day, but this is not striking until the third week; (3) five weeks are required for cicatrization to develop to a sufficient extent to prevent rupture; and (4) firm healing by vascularized scar tissue may be observed eight weeks after onset.

Experimental coronary occlusion was attempted even before cardiac infarcts had been recognized at autopsy. The first of these attempts was probably in 1698, only about seventy years after Harvey's description of the circulation of the blood. In that year Chirac⁴ tied the coronary artery of a dog and found that the heart stopped beating almost immediately thereafter. Similar experiments were described by Erickson,⁵ in 1842, and by Cohnheim and von Schulthess-Rechberg,⁶ in 1881. In all of these early experiments the animals survived only a few minutes, and the observations made on the heart were of necessity physiologic rather than pathologic. The last two authors did, however, note that the portion of the heart muscle nourished by the occluded blood vessel became at first pale and soon afterwards a more livid blue.

In 1893, Kolster,⁷ using an improved operative technique and tying only a small branch of a coronary artery, was able to keep some of his animals alive for periods varying from one day to one year and five months. He described such artificially produced lesions in a series of 12 dogs and demonstrated that the infarcts may heal by a process

similar to that now known to occur in man. The infarcts that he produced were not, however, complete infarcts. This was probably because only a small-sized vessel was occluded. With the histologic technique which he used, a satisfactory interpretation of the details of the process of healing was impossible.

Baumgarten,⁸ in 1899, published an excellent discussion of experimental coronary occlusion but devoted more space to the physiologic than to the morphologic aspects of the problem. He used both cats and dogs, ligating various branches of the left and right coronary arteries. In this way, he was able to discover which areas of the myocardium obtained their nourishment from these blood vessels. Gross and histologic descriptions were given of the lesions produced in eight cats and six dogs. The survival periods varied from twenty-two hours to seven months. The acute infarcts were described as white, or whitish-yellow, opaque, and flaccid. In only three cases were the infarcts hemorrhagic. At the end of two weeks they became white and began to contract, and at seven months the infarct was converted into a thin, white, semitransparent, glistening membrane. Histologically, coagulation necrosis was fully developed after twenty-four hours. At three days, leucocytic infiltration was found, and there were signs of connective tissue proliferation along the margins of the infarct. By the end of fourteen days, connective tissue with many capillaries traversed the whole infarct, and the necrotic muscle had largely disappeared. The next and oldest infarct described was not very satisfactory in that it was only partial. It showed normal muscle traversed by bands of connective tissue. No difference in the process of healing was noted in the two types of animals used.

By far the most thorough and satisfactory of the studies of experimental myocardial infarction was published by Karsner and Dwyer,⁹ in 1916. In order that their observations can be compared with ours on human material, we will give them in some detail.

Dogs were used, and in each the descending branch of the left coronary artery was tied. The dogs were killed after various lengths of time, and in this way a graded series of infarcts was obtained. The ages of the infarcts were one-half hour, 12 hours, 1 day, 2 days, 3 days, 5 days, 6 days, 11 days, 14 days, 18 days, 61 days, and 70 days. Careful gross and microscopic descriptions of each stage were given.

Grossly, the first recognizable change was pallor of the affected area. The infarct became gradually more sharply defined. At two days, it seemed dry and granular, and, at three days, the center was mottled with dusky red areas while the endocardial and pericardial surfaces were a gray-yellow. By five days the infarct was sharply defined, somewhat thinned, and surrounded by a fine line of reactionary hyperemia. The eleven-day infarct was mottled yellow gray and dusky red and surrounded by a thin gelatinous border. At eighteen days this

border had become much thicker. The picture at sixty-one days was one of complete fibrosis, although minute yellow dots of necrotic material could still be seen. After seventy days only a fibrosed scar was found.

The histologic changes were as follows. In the earliest infarct, one about a half-hour old, ill-defined areas showing interstitial edema, congestion, and small hemorrhages were found. The cross striations of the muscle fibers were decreased. By twelve hours there were also areas of hyaline necrosis of the muscle fibers, pyknosis or disappearance of muscle nuclei, polymorphonuclear leucocytic infiltration, and a few mononuclear cells. In the twenty-four-hour infarct, hyaline necrosis of the muscle was increased, and these necrotic fibers were becoming fragmented and invaded by polymorphonuclear leucocytes. Also, the connective tissue around the blood vessels and beneath the endocardium contained mitotic figures. These fibroblasts had noticeably increased in number by forty-eight hours, and after five days there was a well-defined zone of these cells at the periphery of the infarct. At six days definite plasma cells were found among the infiltrating cells. From eleven to eighteen days, the necrotic muscle gradually decreased in amount and was slowly replaced by connective tissue. Mitotic figures in the fibroblasts gradually decreased in number. At eighteen days the infarct had become a well-defined scar, although necrotic muscle, monocytes, polymorphonuclear leucocytes, and lymphocytes were still present. Very small areas of necrotic muscle were still present at sixty-one days and seventy days, but the connective tissue had become very much condensed and the cellular infiltration had disappeared.

From the preceding discussion it can be seen that, save for the descriptions given by Levine, the only work that has taken the time element in healing into consideration has been carried out on experimental animals. The pathologic discussion given by Levine, although excellent, does not cover a sufficient number of cases and is not detailed enough for adequate conclusions. The experimental studies allow one to conclude that infarcts similar to those seen in man can be produced in animals, and that these infarcts heal by a process very like that which occurs in the human. It does not seem fair to state, however, that this process goes on at the same speed as in man, for it is obvious that the infarcts in the animal must be smaller because of the small size of the heart itself, and also that the remaining collateral circulation in the animal heart is relatively more adequate because no marked degree of arteriosclerotic change is present.

MATERIAL OF PRESENT STUDY

The material used in this investigation consisted of patients who showed a myocardial infarct at autopsy and had been thoroughly

studied clinically, so that conclusive evidence as to the onset, and therefore the age, of the infarct was available. In order to obtain an adequate number of such cases it was necessary to use material from several hospitals. We are grateful to the following Boston Hospitals for their aid in this study: Peter Bent Brigham, Beth Israel, Boston City, and Massachusetts General.

Although the original group consisted of more than 100 cases, only seventy-two of these were found to be entirely satisfactory from all points of view. The distribution of these cases from the standpoint of the age of the infarct can be seen in Table I. As is shown by this

TABLE I
AGE DISTRIBUTION OF THIS SERIES OF MYOCARDIAL INFARCTS

FIRST WEEK		SECOND WEEK		THIRD WEEK		FOURTH WEEK	
DAYS	NO. OF CASES	DAYS	NO. OF CASES	DAYS	NO. OF CASES	DAYS	NO. OF CASES
1	11	8	0	15	0	22	2
2	5	9	3	16	1	23	2
3	3	10	3	17	0	24	0
4	2	11	0	18	2	25	1
5	2	12	2	19	0	26	2
6	2	13	1	20	0	27	0
7	2	14	2	21	2	28	1
Total	27		11		5		8*

FIRST MONTH		SECOND MONTH		FIRST HALF YEAR		SECOND HALF YEAR		YEARS	
WEEKS	NO. OF CASES	WEEKS	NO. OF CASES	MONTHS	NO. OF CASES	MONTHS	NO. OF CASES	YEARS	NO. OF CASES
1	27	5	3	1	55	7	0	1	66
2	11	6	1	2	1	8	0	2	1
3	5	7	0	3	1	9	0	3	1
4	12*	8	0	4	1	10	1	4	3
				5	0	11	0	11	1
				6	1	12	3		
Total	55		4	Total	62		4	Total	72

*The clinical age in 4 cases was given as one month.

table, a sufficiently satisfactory distribution of infarct ages occurred in the period of the first five weeks, but thereafter only more or less sporadic representation was found. Old, completely healed infarcts were also comparatively easy to find, and in some of these cases the age of the infarct could be computed from the history. It was very difficult, however, to obtain data from patients dying in the period of from six weeks to eleven months after the occurrence of the infarct.

The following general features of the group are of some interest, and, when compared with other larger series, show that our group was representative.

1. Age of patient. The average age of the patients was 59.2 years; the youngest was 42 years of age, the oldest, 79 years.

2. Sex. Seventy-four per cent of the patients were males and 26 per cent were females.

3. Weight of the heart. The average weight was 503.5 gm.; the smallest weighed 300 gm., and the largest, 880 gm. It was thought that the weight of the heart in relation to the age of the infarct might be of some interest. Four hearts with infarcts 1 to 2 months old averaged 450 gm. in weight, five hearts in which the infarct was 2 to 6 months old averaged 500 gm., and eighteen hearts in which the infarct was more than 6 months old averaged 570 gm. These data suggest that an infarct, *per se*, may lead to cardiac hypertrophy.

4. Cardiac rupture. This had occurred in eight cases. None of these infarcts was more than 2 weeks old. The average weight of these eight hearts was 484 gm.

5. Diabetes mellitus. This disease was present in nine cases. The average age at time of death in this group was 58 years.

6. Coronary arteries. In practically all of these cases there was a moderate to marked generalized coronary atherosclerosis in addition to occlusion of a branch. In the original group, definite thrombi were found in seventy instances. The distribution of these thrombi was as follows:

a. Left coronary artery	59 cases
Descending branch	52
Circumflex branch	4
Septal branch	3
b. Right coronary artery	8 cases
c. Right and left coronary arteries	3 cases

7. Location of the infarct. As would be expected from the location of the occlusions, the majority of the infarcts involved the apex of the left ventricle alone, or this and the interventricular septum. In fifty-four of the cases the location of the infarcts was described in sufficient detail so that a satisfactory idea of their position and extent could be obtained. The distribution of these is given in tabular form below:

Left ventricle	
Apex	24
Apex and septum	22
Base	5
Base and septum	2
Right ventricle	1

8. Valve lesions. Aortic stenosis, probably caused by arteriosclerosis, was present in four cases, and in one there was a rheumatic mitral stenosis.

In many of the cases the only histologic material available consisted of the routine autopsy sections of the heart. Most of these had been stained with phloxine methylene blue, a few with hematoxylin and eosin. Material fixed in Zenker's fluid and in formalin was, however, obtainable in the cases representing the more important ages of the

infarct, and in these cases phosphotungstic acid hematoxylin, aniline blue connective-tissue, iron, and fat stains were made.

The histologic changes will be first described and then correlated with the gross appearances. In dealing with the histologic picture, a discussion of the appearance and progress of each of the histologic features will be first presented, and then an attempt made to describe the criteria characteristic of the various ages of the infarcts.

HISTOLOGIC DATA

Necrosis.—The first result of a stoppage of the blood supply to a portion of the myocardium is necrosis of the muscle fibers and, to a lesser extent, of the connective tissue and smaller blood vessels. Although probably the necrosis of the muscle starts almost immediately, it is difficult or impossible to find any definite histologic evidence of it until five or six hours have elapsed. There are several changes that then become evident. The most striking and generalized of these is that the involved muscle fibers begin to appear somewhat hyaline and take a much deeper acid stain. In a hematoxylin and eosin, and, to a much more marked extent, a phloxine methylene blue preparation, they are a much brighter red. The striations become somewhat more difficult to see, but do not disappear, and can even be found in later stages when the muscle fibers have been broken into small fragments and have undergone phagocytosis by histiocytes.

Other signs of necrosis occur in single fibers or small groups of fibers. In these the striations cannot be made out; the fibers are swollen and contain eosinophilic granules of various sizes, or large, irregular cross bands.

If the thrombosis is complete the necrosis will be found to occur uniformly throughout the infarct, save for a thin layer of surviving tissue along the endocardium which extends along the Thebesian veins up into the myocardium. This layer is about 0.3 to 0.5 mm. in thickness. Its existence must be explained by assuming that nourishment passes directly through the endothelium from the blood present in the lumen of the ventricle and in the veins. It was also found to occur in the experimental infarcts described by Karsner and Dwyer.

Necrotic muscle is a constant constituent of these infarcts and, although gradually removed, may persist for a long period of time. It was found in two out of five infarcts at 1 month of age, in two out of three at 5 weeks, in one at 6 weeks, and in one at 4 months.

Hemorrhage.—Hemorrhage into infarcts is somewhat variable. It frequently occurs, but is usually found to be focal rather than spread diffusely throughout the infarct. On histologic examination, the erythrocytes are most frequently found to be in distended venules and blood capillaries, while true extravasation around the muscle fibers is comparatively rare. As these hemorrhages become older the erythrocytes

break up, and eventually the hemoglobin which they contained is taken up by macrophages in the form of hemosiderin. In the past there has been much discussion as to whether myocardial infarcts should be classified as anemic or hemorrhagic. The true answer to this question is probably that they may show features of both and are rarely, if ever, purely one or the other.

Fat.—The amount of fat present in an infarct is to a large extent dependent on how suddenly the thrombosis or occlusion took place. If the area of myocardium that is infarcted has previously had an insufficient circulation, fatty degeneration will have occurred, and the infarcted muscle contains a large number of small fat droplets. If, on the other hand, the muscle was entirely normal before it was infarcted, it shows only a small amount of fat. In this type of infarct the majority of the fat will be found on the periphery, adjacent to normal fibers, while the central fibers show little or none. The probable explanation of this distribution is that these peripheral fibers get partial, but insufficient, nourishment from the adjoining normal tissue. The amount of fat decreases as the infarct gets older and is removed at the same time as the necrotic muscle fibers.

Infiltration with Polymorphonuclear Leucocytes.—As a result of the necrosis of muscle, polymorphonuclear leucocytes are attracted and soon begin to infiltrate around and into the necrotic muscle. This apparently begins about as soon as signs of necrosis can be identified in the muscle. This infiltration starts peripherally and spreads centrally; it is much more active on the epicardial side and in those portions adjacent to the uninvolved muscle with intact vasculature than on the endocardial surface. In the earliest stages the polymorphonuclear leucocytes are found in the interstitial tissue and around the blood vessels. From here they infiltrate diffusely around and, to some extent, into the necrotic fibers. The power to penetrate seems somewhat limited, and in large infarcts, particularly when the remaining circulation is poor, the central portions of the infarct never become infiltrated. Sometimes a sharp line of demarcation can be found between the infiltrated areas and those that are not, suggesting that the infiltrative power of the leucocytes is definitely limited.

The first signs of infiltration are seen in infarcts during the first twenty-four hours. The amount of infiltration progressively increases during the first four days. At about forty-eight hours some of the polymorphonuclear leucocytes start to undergo degenerative changes, as evidenced by the loss of sharpness of their outlines and the accumulation of fragments of nuclear debris. By the fifth or sixth day many of the polymorphonuclear leucocytes have become necrotic and thereafter gradually disappear. By the fourteenth day they have practically completely disappeared.

For some reason not understood, after the removal of the peripheral muscle fibers, in the process of healing, the remaining central necrotic

muscle provokes little or no fresh infiltration of polymorphonuclear leucocytes, even when the collateral circulation has developed to such a point that fresh capillaries are present adjacent to it.

The exact function of the polymorphonuclear leucocytes is difficult to explain. They do not phagocytose the necrotic muscle. It is possible that they may produce some enzyme which aids in the final breakdown and phagocytosis of the muscle fibers, but they produce no definite change in the muscle fibers that can be recognized histologically.

Infiltration by Eosinophiles.—From the fourth to the eighteenth day, varying numbers of eosinophiles may be found in the areas of infiltration.

Ingrowth of Blood Vessels and Connective Tissue Cells.—Newly formed blood capillaries can be found growing into the infarcted area, beginning on about the fourth day. This process starts on the periphery and extends centrally. When the infarct involves the endocardial surface, only slight ingrowth of blood vessels and connective tissue can be found occurring from this side. The extent of this vascularization seems to be limited to a certain degree. It takes place quite rapidly on the periphery and more slowly in the center. In large infarcts which show necrotic central masses of muscle, frequently no vascularization of this tissue can be demonstrated even at periods when the periphery of the infarct is well healed. These newly formed blood vessels never seem to attain very large size.

Accompanying these blood vessels, fibroblasts can be seen to grow into the infarcted area. These frequently show mitotic figures. While still young, they show, in the phloxine methylene blue preparation, a basophilic staining of their cytoplasm. These basophilic fibroblasts have been found in infarcts ranging in age from 4 to 23 days.

It is very difficult to be sure whether all of the fibroblasts found in the healed stage of the infarct are the result of this ingrowth, or whether part of them represent the original fibroblasts of the stroma of the heart which have survived while the muscle fibers have not.

When one compares the healing of cardiac infarcts with the healing of infectious lesions, one discovers that the fibrin which is present in the latter is quite strikingly absent in the former. The ingrowth of connective tissue and blood vessels cannot be explained as an organization of fibrin; the exact stimulus for it is not known.

The Removal of the Necrotic Muscle, and Infiltration by Pigmented Macrophages.—The removal of the necrotic muscle is the result of phagocytosis by mononuclear cells, probably histiocytes. This process starts at the periphery and begins simultaneously with the ingrowth of blood vessels and connective tissue. The histiocytes penetrate the necrotic muscle fibers and gradually phagocytose the muscle. They can be found containing reddish fragments of muscle. These fragments are apparently dissolved in the cell, and they disappear. The waste, or

lipofuscin pigment of the muscle, is also phagocytosed, but it cannot be dissolved and remains in the cell. Because of this, any healing infarct can be found to contain numerous pigmented macrophages.

Most of the pigment in these phagocytic cells was formerly present around the nuclei of the muscle fibers. It is yellow-brown in color and does not give a positive iron reaction, but does stain faintly with scarlet red. Some of the cells, however, do contain iron-positive hemosiderin granules resulting from the breakdown of erythrocytes in hemorrhagic areas. Frequently both types of pigment are present in a single macrophage.

The removal of the necrotic muscle occurs much more rapidly at the periphery than it does centrally. In a 10-day infarct the peripheral muscle fibers are usually completely removed for a distance of about 1 mm. Active absorption can be demonstrated to be taking place in infarcts as old as 6 weeks. After this time necrotic muscle may still be present, but signs of absorption are difficult to demonstrate.

The pigmented macrophages remain for a time after actual absorption has ceased. As the infarct becomes older they decrease in number, and in infarcts 1 to 2 years old they have practically disappeared.

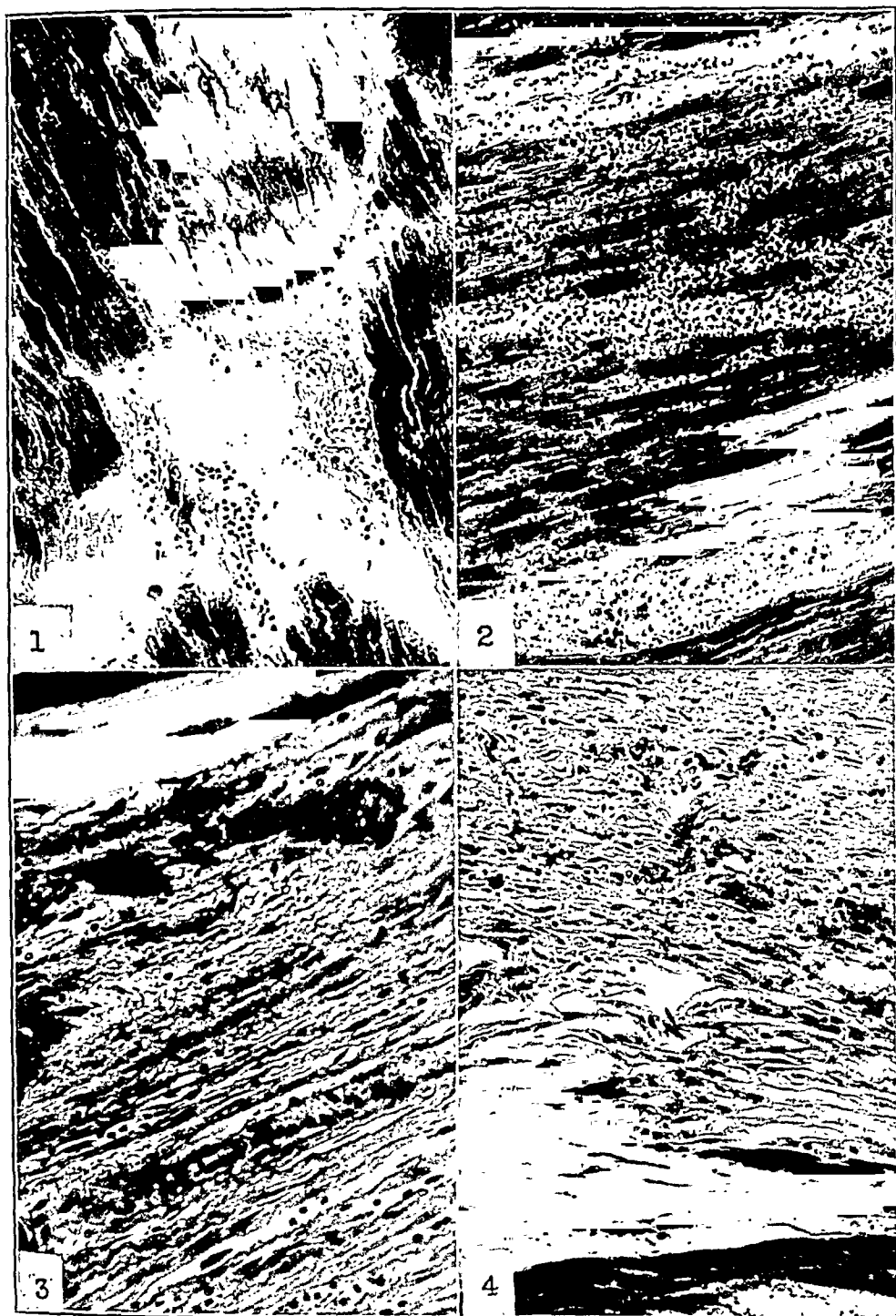
Lymphocytes and Plasma Cells.—Foci of lymphocytes and plasma cells can be found in infarcts as soon as absorption of muscle fibers starts. They are never as numerous as the macrophages. They also decrease in number as the infarct becomes older and usually disappear at about the same time as the pigmented macrophages.

Collagen Formation by the Fibroblasts.—As the newly-formed connective tissue in the infarct becomes older, increasing amounts of intercellular collagen fibers are formed. It is the formation of this collagen that increases the strength of the fibrous scar. Fine, newly-formed collagen fibers are usually found first at about twelve days. At three weeks the collagen is moderately prominent, particularly at the periphery, and at about two to three months it has reached its maximum.

The Pericardium.—In many infarcts, particularly those in which the muscle beneath the epicardium is involved, a fibrinous pericarditis can be found after twenty-four hours. This begins to become organized about the eighth or ninth day and, unless of unusual thickness, or-

Fig. 1.—Photomicrograph, medium power, 24-hour infarct. The muscle fibers are swollen, opaque, and take an acid stain. The nuclei are difficult to make out. Many muscle fibers have a banded, granular appearance. There are a slight degree of polymorphonuclear leucocytic infiltration in the interstitial connective tissue and very early invasion between the muscle fibers.

Fig. 2.—Photomicrograph, medium power, five-day infarct. Necrosis of muscle fibers is shown by deep staining with eosin. Nuclei are difficult to make out. There is marked infiltration by polymorphonuclear leucocytes between, and, to a certain extent, into, the necrotic muscle fibers. Particles of nuclear debris in areas of infiltration have arisen as a result of the necrosis and breakdown of the polymorphonuclear leucocytes. There is periphery of infarct above and in central portion below. Infiltration tends to decrease toward center.



Figs. 1 and 2. (See opposite page for legends.)

Fig. 3.—Photomicrograph, medium power, fourteen-day infarct. Peripheral muscle fibers have been completely removed. Fairly numerous, fine collagen fibers are present. There is infiltration with pigmented macrophages and lymphocytes.

Fig. 4.—Photomicrograph, medium power, five-week infarct. Field chosen to show histologic picture adjacent to central necrotic muscle. No acute reaction is present. A few histiocytes appear next to the necrotic muscle fibers which are apparently phagocytosing them. Collagen is quite prominent except adjacent to the necrotic muscle. A few lymphocytes and pigmented macrophages are present.

ganization should be complete in about four weeks after the onset of the infarction. (See Table II.)

TABLE II
ORGANIZATION OF PERICARDIAL LESION

	UNORGANIZED	ORGANIZING	ORGANIZED
2 days	1		
3 days	2		
4 days	1		
5 days	2		
9 days		3	
10 days		1	
12 days	1	1	
13 days			2
23 days			1
26 days			8
1 month		1	

The Endocardial Thrombus.—In our experience, the occurrence and state of organization of an endocardial thrombus have proved less reliable than the pericardial reaction as a means of judging the age of an infarct. Endocardial thrombi occur as early as the fifth day. Beginning organization is found on the ninth day, and complete organization, on the sixteenth day. Fresh or only partially organized thrombi are, however, found in comparatively old infarcts. Because of this we feel that at least some of the mural thrombi occur, not as a direct result of the infarct, but as a secondary result of a later dilatation of the heart. This is shown in Table III.

TABLE III
ORGANIZATION OF MURAL THROMBUS

	UNORGANIZED	ORGANIZING	ORGANIZED
4 days	1	1	
5 days	2		
6 days	1		
9 days		1	
10 days		1	
12 days		2	
14 days			1
16 days			1
23 days		1	
26 days			1
4 weeks		3	
5 weeks		1	1
3 months		1	
10 months			1
3 years			1

CHARACTERISTIC FEATURES OF INFARCTS OF VARIOUS AGES

Even when one keeps the above-described criteria in mind, it is not always easy to judge the age of an infarct from the histologic section. This is particularly true of the infarcts that are three or more weeks old. To judge the age of an infarct, it is very important that the

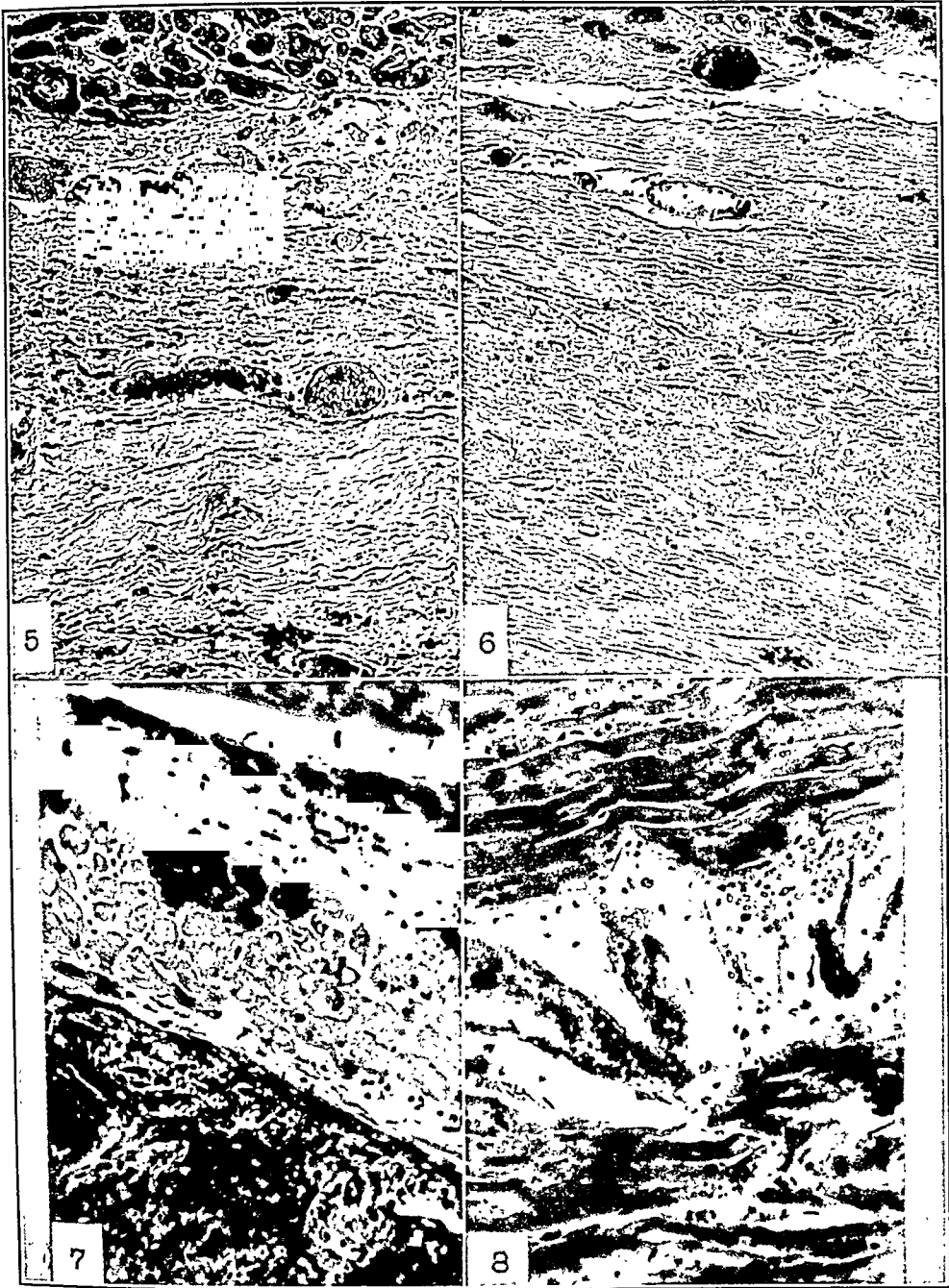


Fig. 5.—Photomicrograph, medium power, three-month infarct. Periphery is shown with normal fibers above. In the infarct, collagen has become very dense and prominent. The vessels are still moderately prominent. Infiltration of cells has practically disappeared.

Fig. 6.—Photomicrograph, medium power, four-year infarct. Normal muscle is shown above. Infarct consists of very old, dense, scar tissue. Little can be seen in scar but very thick collagen bundles. Cell nuclei are rare, and tissue is relatively avascular.

Fig. 7.—Photomicrograph, medium power, five-day infarct. Endocardial surface is shown. Below is an unorganized mural thrombus. There is a band of uninvolved muscle above this which has been spared as a result of obtaining nourishment from the ventricular cavity. Dark-staining necrotic muscle is above this. Note that practically no infiltration has occurred from the endocardial surface.

Fig. 8.—Photomicrograph, medium power, ninety-six-hour infarct. Periphery of infarct shows beginning proliferation of blood vessels. Small capillary sprouts can be seen growing in towards the infarcted area.

material for microscopic examination be taken from the proper area. As has already been pointed out, healing takes place at different rates of speed in various portions of the infarct. It is slowest in the center and most rapid at the periphery, particularly in those areas adjacent to the most effective collateral circulation. A section which shows both uninvolved musculature and the edge of the infarct is the most satisfactory.

When such a section is available one should be able to date infarcts with a fair degree of accuracy. The histologic features that should be found in the infarcts of various ages are the following:

First Week.—During the first twenty-four hours, necrosis of muscle should be found, with slight polymorphonuclear leucocytic infiltration at the periphery. From the second to the fourth day the degree of this infiltration should increase progressively. In the four-day infarct the periphery should show marked infiltration with polymorphonuclear leucocytes, with degenerative changes and signs of necrosis in many of those infiltrating cells. On the fourth or fifth day the first signs of removal of muscle fibers appear. Blood capillaries and connective tissue can be found penetrating the infarct from the periphery. Single fibers, or small clumps of fibers, may have undergone phagocytosis and removal by the seventh day.

Second Week.—It is during this stage that the removal of the peripheral muscle fibers becomes a prominent histologic feature. By the tenth day there is a peripheral zone, 1 mm. or more in thickness, from which the necrotic muscle fibers have been almost completely removed. As a result, numerous pigmented macrophages are found. The ingrowth of blood vessels and connective tissue has become quite prominent. The fibroblasts have a curious basophilic character. Moderate numbers of eosinophiles, lymphocytes, and plasma cells may be found. Active phagocytosis and removal of fibers occur along the edge of the remaining necrotic muscle. By the end of the second week the muscle fibers should be almost completely removed from small infarcts (3 to 4 mm. in diameter). Polymorphonuclear leucocytes have practically disappeared.

Third Week.—During the third week the removal of muscle fibers still continues in large infarcts. Pigmented macrophages are numerous. Eosinophiles are still present, but decreasing. The basophilia of the fibroblasts is also becoming less marked. Plasma cells and lymphocytes may be fairly prominent. In addition to these features, the first signs of collagen formation may be found in the form of fine collagen fibers. These are first produced by the fibroblasts at the periphery.

Fourth to Sixth Week.—During this stage, recognition of the age of the infarct is largely dependent upon the amount of collagen that has been formed by the connective tissue cells. Therefore, accurate dating

is difficult or impossible. A necrotic central mass of muscle may still be found during this period, and usually some signs of active removal of this material are still present. By the end of this period, collagen is quite a prominent feature in the infarct. The whole scar is definitely contracted, and the vascularity and infiltration by pigmented macrophages and lymphocytes are beginning to decrease.



Fig. 9.—Photomicrograph, low power, ten-day infarct. Complete cross section of wall of left ventricle. Infarct has involved the whole wall. Dark-staining tissue in central portions consists of necrotic muscle fibers without reaction. Along both upper and lower borders of this is a narrow band in which the muscle has been almost completely removed, showing that healing is taking place from both endocardial and epicardial sides. A similar process can be seen in the papillary muscles, where dark-staining necrotic muscle is present in the central portions. There are present a fibrinous pericarditis and an endocardial thrombus, both of which show early organization.



Fig. 10.—Photomicrograph, low power, sixteen-day infarct. Wall of left ventricle. A dark central area of necrotic fibers which are not as yet removed is shown. At upper left is a wedge-shaped area of uninvolved muscle. Pale areas are those in which muscle has been completely removed. Infarcted area has not yet shrunk appreciably. Note thin area of uninvolved muscle along endocardium. There is a completely organized endocardial thrombus at lower right.

Sixth Week to Second Month.—During this period the collagen becomes more and more dense, until, at the end of two months, this process has about reached its maximum. Except in very rare cases, the muscle fibers are completely removed by the end of this period. Cellular infiltration is markedly diminished. The infarct is now practically healed.

Second Month On.—Very little further change takes place, although some pigmented macrophages and lymphocytes may be found up to one year.

The findings described above are summarized in Table IV.



Fig. 11.—Photomicrograph, low power, five-week infarct. Central islands of necrotic muscle are still present. In areas surrounding these, muscle fibers have been completely removed. The scar is becoming dense and contracted. Note sharp areas of demarcation between necrotic muscle and healed areas. A dense, completely organized endocardial thrombus and marked sclerosis of blood vessels are present. In two areas which apparently have better vascularization, muscle fibers have been removed throughout the entire thickness of the myocardium.

GROSS APPEARANCE

Attempts were made to discover the gross characteristics of infarcts of various ages. For this purpose the only available material in the majority of the cases consisted of the gross descriptions given in the autopsy protocols. The results were discouraging, save for a few generalities. Most infarcts were described as soft, until an age of two to three months was reached. From that time on they were usually noted as firm and contracted. The descriptions of the colors were even less helpful. Most early infarcts were described as yellow, or red, or pale, and no uniformity was reached until the infarcts were about three months old, when they were depicted as white, fibrous scars.

As a result of these difficulties, myocardial infarcts from which gross specimens had been preserved and those occurring in current autopsies were observed, and the gross and microscopic pictures correlated. This series is as yet too small for entirely satisfactory conclusions. It is sufficient, however, to allow us to say that most of the

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features described histologically can also be seen grossly if the infarcts are examined closely enough.

The earliest change after infarction is that the involved area of myocardium appears paler and dryer than normal. Sometimes, focal, blotchy, red-purple areas of hemorrhage are found. This is essentially the picture during the first forty-eight to seventy-two hours. At first the changes are very slight and difficult to make out, but they become progressively more distinct.

As soon as any degree of leucocytic infiltration has occurred, the infiltrated areas become yellow-brown in color. In an infarct about four days old a fine yellow line or border can be seen around its periphery. As the infiltration becomes more extensive this yellow band becomes broader in extent, and sometimes even a yellow-green in color. This is particularly true of infarcts six to eight days old.

The removal of muscle fibers shows itself in two ways. In the first place, a reddish-purple zone is found around the periphery of the infarct as the result of the formation of granulation tissue. The color is due to the presence of numerous newly-formed capillaries filled with erythrocytes. In the second place, the actual removal of fibers results in a shrinkage in the volume of the whole infarct. Therefore, the thickness of the myocardium in the infarcted area decreases, and a definite depression can be seen around the periphery of the infarct when it is viewed in cross section. This process first becomes apparent grossly after eight to ten days.

Continued healing results in an increase in the width of this band of depressed granulation tissue. The central mass of necrotic muscle gradually decreases in amount and assumes a pale, red-brown color. At three to four weeks, usually only small islands of necrotic muscle are found, and these are completely surrounded by granulation tissue.

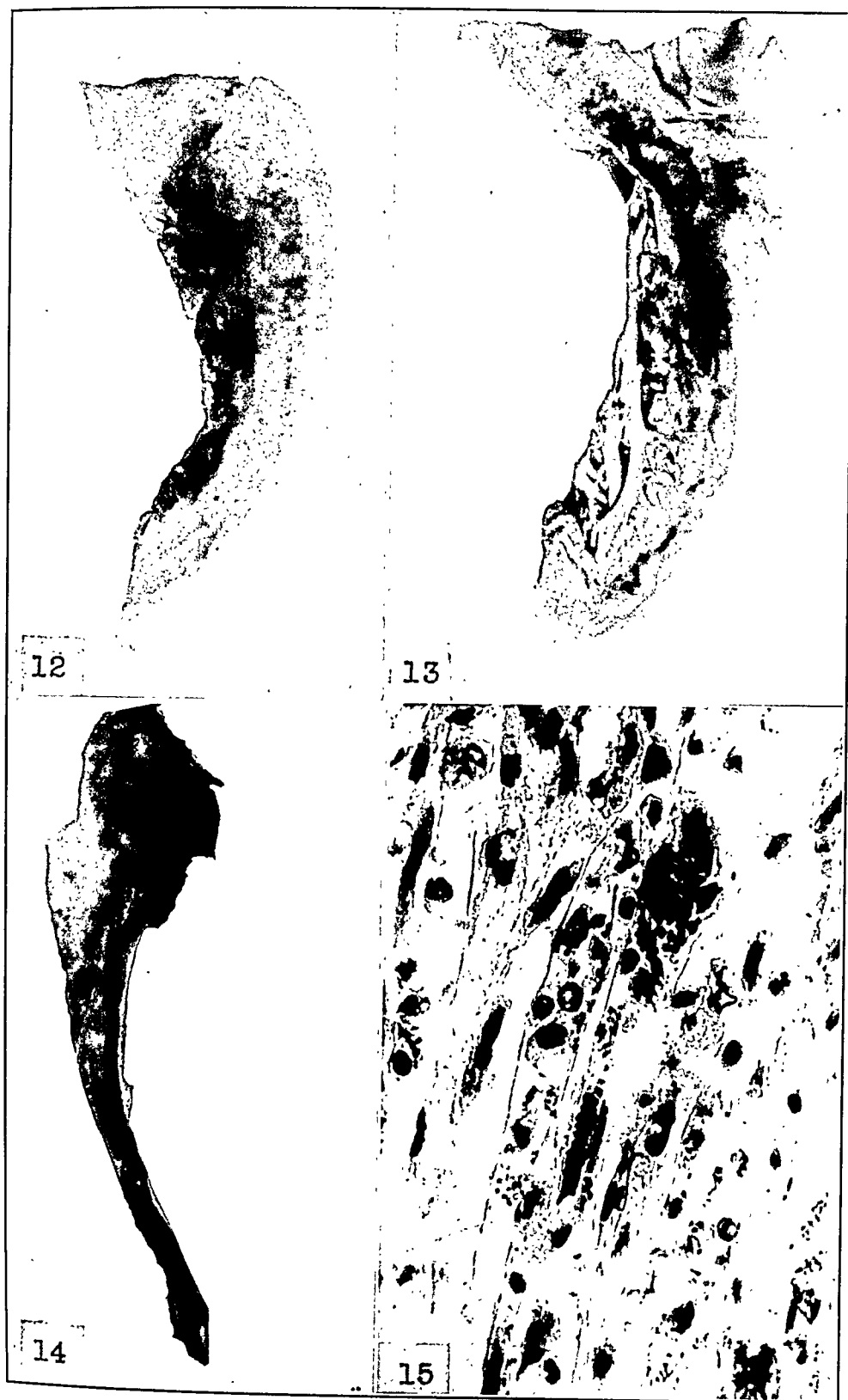
As this granulation tissue becomes older its collagen content increases, and the capillaries are compressed and less prominent. As a result of this, it becomes much paler and appears somewhat gelatinous. As the infarct becomes older it contracts more and more and eventually is transformed into a shrunken, firm, white, fibrous scar. It presents this appearance after about two to three months, and grossly no further change can be seen to take place.

Fig. 12.—Gross photograph, seven-day infarct. Longitudinal section of wall of left ventricle. Epicardial fat is shown along right border. Infarcted muscle stands out as irregular pale areas, in contrast to normal, darker, uninfarcted muscle. There is a fresh thrombus on the endocardial surface.

Fig. 13.—Gross photograph, fourteen-day infarct. Longitudinal section of wall of left ventricle with epicardial fat along right border. The unremoved infarcted muscle can be seen as pale islands, surrounded by a dark, depressed zone of granulation tissue. Here peripheral muscle fibers have been removed and replaced by blood vessels and connective tissue. The myocardial wall is somewhat decreased in thickness.

Fig. 14.—Gross photograph, infarct 6, or more, months of age. Longitudinal section of wall of left ventricle. Epicardial fat may be seen to left. The myocardial wall is very shrunken and consists of pale scar tissue. Necrotic muscle is completely removed.

Fig. 15.—Photomicrograph, high power, ten-day infarct. Detail, to show method of removal of necrotic muscle. Fibers fragmented but have not lost cross striations. Fragments are surrounded by histiocytes which seem to dissolve and phagocytose them. Polymorphonuclear leucocytes are rare at this stage.



Figs. 12 to 15. (See opposite page for legends.)

Similar changes occur in the pericardium and endocardium. The early fibrinous pericarditis can be seen as a thin, nonglistening, and easily detached layer of fibrin. As this becomes organized it adheres firmly to the epicardium and is eventually transformed into a focal, white area of fibrosis. In the same way the endocardial thrombus becomes more adherent and is gradually transformed into a thickened plaque of connective tissue which is eventually covered by endothelium.

FURTHER COMMENTS

Discrepancies.—In this group of infarcts a certain number were found which seemed too young or too well healed for their supposed age. A few of these discrepancies were almost too great to be explained at all, but the less marked ones can be accounted for by one or both of the following factors.

1. The size and the location of the infarct have an influence on the rate of healing. Small infarcts heal more rapidly than large ones. Subendocardial infarcts heal less rapidly than those in the center of the myocardium or beneath the epicardium.

2. The rate of healing also seems dependent upon the competency of the remaining circulation. If the coronary vessels show a marked degree of diffuse arteriosclerosis, with narrowing of their lumina, the rate of healing will be slower than it would if the remaining vessels were essentially normal. In the same way, if the circulation in the myocardium is somewhat inadequate as a result of a failing heart or generalized anemia, healing probably will not be so rapid and efficient as when adequate collateral coronary circulation is present.

In the cases in which there were greater discrepancies, we can only assume either that the history was inaccurate, or that two or more infarcts were present in the heart and that the microscopic sections were taken only from the one which had caused no definite symptoms.

Comparison of Healing of Experimental and Human Infarcts.—The process of healing of myocardial infarcts in man is very similar to that of the experimental lesions in the dog's heart, as described by Karsner and Dwyer.⁹ Hemorrhage seems to be somewhat more prominent in the experimental lesions, and the only pigment found in them is hemosiderin. This is explainable on the ground that one would expect little or no waste pigment to be present in the heart of a young and healthy dog. A foreign-body giant cell reaction around necrotic muscle fibers is present in the experimental infarcts. This is rarely, if ever, seen in the human lesion.

Outside of these rather minor features, the chief difference is in the rate of healing of the infarcts. On the whole, the experimental lesions heal more rapidly than those seen in man. Signs of blood-vessel and connective-tissue proliferation are found at the end of forty-eight hours in the dog and not until ninety-six hours in man.

After eighteen days the experimental lesions are fairly well contracted and fibrosed, although remnants of necrotic muscle are still found at a much later date. In the human infarcts considerable necrotic muscle is still likely to be present after three weeks, and collagen, although present in some degree, is not as yet a very prominent feature.

The rate of healing of the experimental lesions is very similar to that in man when the human infarcts are small and the remaining myocardial circulation is in good condition. That human infarcts are likely to be larger is obvious when one considers that the wall of the left ventricle of a dog rarely measures over 6 mm. in thickness, whereas in human hearts, particularly the hypertrophied ones from patients who had had hypertension, the left ventricular wall is from 1.5 to 2 cm. thick. Also, the remaining intact coronary circulation is much more likely to be wholly normal in the dog. These two factors probably explain the difference in the speed of healing.

One feature which is observed both in the experimental and in the human lesions may have some clinical significance. This has already been mentioned; it is the fact that there is always a thin layer of surviving myocardium along the endocardial surface, extending into the myocardium along the Thebesian veins. As this is less than half a millimeter in thickness, it probably plays no significant role in preventing rupture, but when one remembers that many of the finer branches of the conduction system lie in this region it does perhaps explain why cardiac arrhythmias are comparatively rare in cases of myocardial infarction.

This observation is also of interest when considered in relation to the formation of intracardiac thrombi on the endothelium over the infarcted area. Even when well-formed thrombi are beginning to undergo organization, a thin layer of surviving myocardium can usually be found lying between the thrombus and the infarcted myocardium. Although one cannot make out a definite layer of endothelial cells beneath such thrombi, it would seem logical to believe that its disappearance was more likely to be the result of the thrombus formation than the cause of it. It does not seem probable that specialized cells such as cardiac muscle fibers should survive ischemia, while unspecialized endothelial cells should not. Also, along the Thebesian veins, where a thin layer is also spared, but where thrombus formation rarely occurs, both muscle and endothelium survive. Therefore, it would seem more logical to interpret the thrombus as a result of local dilatation of the heart plus stagnation of the blood in this area, than as a reaction to the necrosis of the endothelium.

Cardiac Rupture.—The problem of the time of rupture of an infarcted myocardium is important. From a theoretical standpoint, sev-

eral factors seem to be of significance. Necrotic tissue is undoubtedly less resistant than viable tissue. Therefore, rupture would be expected to occur when necrotic tissue is most abundant and before any degree of replacement by connective tissue and blood vessels has occurred. Histologically, necrotic tissue is most prominent from the second to the sixth day. The influence of polymorphonuclear leucocytic infiltration is difficult to judge. It may tend to reduce the resistance of the necrotic tissue by enzymatic digestion of portions of it. If it does produce such an effect, it would reach its maximum between the fourth and sixth days.

Another factor of importance in this connection is the intraventricular pressure. The higher this pressure, the more likely rupture is to occur. When the valves are normal, the intraventricular pressure is dependent on the pressure in the peripheral circulation; valvular abnormalities, particularly aortic stenosis, will, per se, cause it to be high. A preceding hypertension is common. It was present in more than one-third of the cases reported by Levine.³ The same author states that a drop in blood pressure usually occurs at the time that infarction takes place, or soon thereafter, and that the blood pressure does not usually return to as high a level as before, but that in some instances the blood pressure may rise again a few days after the infarction.

In our eight cases of cardiac rupture the blood pressures after infarction were as follows: 173/90, 150/100, 140/80, 130/90, 110/78, 110/70, 90/70, 90/50. It is interesting to note that the only case in this group in which aortic stenosis was associated with infarction and rupture was the last.

After consideration of all of these more or less theoretical aspects, the optimum time for rupture to occur seems to be some time within the first ten days after myocardial infarction.

In our series, the ages of the infarcts at the time of rupture were the following:

1 day	1
2 days	1
3 days	1
6 days	2
7 days	1
9 days	1
12 days	1

The group is, of course, too small to allow extensive conclusions. From Levine's monograph one can take eight or nine additional cases. In his series of forty-seven autopsy cases, rupture occurred in nine. Calculating the age of the infarcts from the histories given, the following data are obtained:

1 day	1
3 days	1
4 days	1
6 days	2
11 days	1
14 days	2
5 weeks	1

Combining these two groups, a series of seventeen ruptured hearts is obtained, with the following distribution:

1 day	2
2 days	1
3 days	2
4 days	1
6 days	4
7 days	1
9 days	1
11 days	1
12 days	1
14 days	2
5 weeks	1

In the combined series, eleven, or 65 per cent, occurred in the first week, and five, or 29 per cent, in the second week.

A group of thirty-four cases of rupture of the heart following myocardial infarction was reported by Benson, Hunter, and Manlove.¹⁰ They did not give sufficient data to enable one to estimate the actual age of the infarcts in their series, but twenty-nine are described as acute infarcts and four as acute infarcts superimposed on old ones; in one case there was dissecting rupture of an aneurysmal dilatation, following infarction which occurred about three months before death.

Combining these figures, it is justifiable to conclude that if a heart is going to rupture after infarction, it is most likely to do so during the first week; it may rupture during the second week; but rupture after the third week is rare, and when it does happen it is usually the result of some complicating factor, such as a fresh infarct.

CLINICAL APPLICATION

Of the greatest importance, of course, is the clinical application of the information that has come from this study of the speed of healing of myocardial infarction. We can now rest assured that in most cases repair proceeds steadily and in a fashion similar to that of scar formation in other parts of the body. In a month's time there is almost complete healing of small infarcts. Large infarcts require a few weeks longer, up to two months, to heal completely. There are rare

instances in which islands of unorganized necrotic muscle may remain longer, more or less as foreign bodies in the midst of myocardial scars; it is not likely that such unresolved lesions play much of a role, since they are surrounded by the thick, strong, fibrous tissue of the scar.

The two points of difference between the healing of a myocardial infarct caused by coronary disease and a traumatic lesion of muscle or bone elsewhere in the body are (1) that the myocardium must continue to function during the process of repair, whereas bone, skeletal muscle, or ligaments are immobilized, and (2) that the blood supply available for the healing of the cardiac lesion may be limited because of widespread narrowing of the coronary arteries. Thus, although it is well known that a small infarct may heal completely and cause little or no abnormality of cardiac size, function, or reserve, despite the lack of all treatment, nevertheless, there is no question that the strain of increased heart work, or even the work of the heart at rest, in some cases, may be too great when the myocardial infarct is large, with resulting cardiac dilatation and even failure. The second point is probably not so significant, for apparently a rich blood supply is not needed to promote good healing; even in the grave cases of our series, in which the patient died relatively early as the result usually of the heart disease itself, and had extensive coronary sclerosis, the healing of the infarct was in active swing from the very beginning.

Thus, our findings support the more or less empirical custom of those who advise for patients with small- to moderate-sized myocardial infarcts, without complications, one month of rest in bed (the first two weeks absolutely complete), and one month of very carefully graded convalescence, with a third month to consolidate recovery and to re-establish good health both of body and mind. To advise less than three weeks in bed is unwise, even for patients with the smallest myocardial infarcts, provided we are sure of the diagnosis; and it is almost equally unwise to advise prolonged bed rest in the absence of complications or when the infarct is not very large, because of the needlessness of so doing and the harm to the patient's health in general and to the morale and happiness of himself and of his family.

SUMMARY AND CONCLUSIONS

Seventy-two autopsy cases of myocardial infarction, in which the age of the infarct could be accurately determined, were studied in order to ascertain the speed of healing of the infarcts.

The characteristic gross and microscopic features of infarcts of various ages are described. Necrosis of muscle and infiltration by polymorphonuclear leucocytes are the important features of the first week. Removal of the necrotic muscle and replacement by connective tissue predominate during the next five weeks. Beginning at about the second week, the newly formed connective tissue lays down in-

creasing amounts of collagen. This collagen gradually increases in amount and becomes more dense. This process reaches a maximum at about three months, and thereafter very little change takes place.

Grossly, evidence of the removal of muscle fibers and their replacement by connective tissue and blood vessels can be seen in the form of a zone of red, depressed tissue surrounding pale brown areas of necrotic muscle. As healing proceeds this increases in extent, while the amount of necrotic muscle decreases. The increase in collagen causes the granulation tissue to become paler and gradually transforms it into a pale, firm, fibrous scar.

The process of healing of human infarcts in our series was compared with that of experimental infarcts produced by other investigators.

The following are the conclusions resulting from this study:

1. The age of an infarct can be judged fairly accurately from the histologic picture during the first three weeks. After this the estimation is not very accurate.

2. The speed of healing is in part dependent upon the size and position of the infarct and in part upon the state of the remaining myocardial circulation.

3. Small infarcts are almost completely healed after five weeks. Large infarcts are completely healed, or undergo no further discernible change, after two months.

4. Rupture of the heart is most common during the first week, may occur during the second week, but is rare thereafter. Histologically, much of the necrotic muscle has been replaced by connective tissue by the end of the first fortnight.

5. The healing of infarcts in human hearts is similar in most respects to that of experimental lesions in animals, except that the process is slower.

REFERENCES

1. Weigert, Carl: Ueber die pathologischen Gerinnungsvorgänge, *Virchows Arch. f. path. Anat.* 79: 97, 1880.
2. Ziegler, Ernst: Ueber die Ursache der Nierenschumpfung nebst Bemerkungen ueber die Unterscheidung verschiedenr Formen der Nephritis, *Deutsches Arch. f. klin. Med.* 25: 589, 1880.
3. Levine, Samuel: Coronary Thrombosis; Its Various Clinical Features, *Medicine* 8: 245, 1929.
4. Chirac, P.: *De motu cordis, Adversaria Analytica*, p. 121, 1698.
5. Erickson, John E.: On the Influence of the Coronary Circulation on the Action of the Heart, *London Med. Gazette* 2: 561, 1842.
6. Cohnheim, J., and von Schulthess-Rechberg, A.: Ueber die Folgen der Kranzarterienverschiessung für das Herz, *Virchows Arch. f. path. Anat.* 85: 503, 1881.
7. Kolster, R.: Experimentelle Beiträge zur Kenntnisse der Myomalacia Cordis, *Skandinav. Arch. f. Physiol.* 4: 1, 1893.
8. Baumgarten, W.: Infarction of the Heart, *Am. J. Physiol.* 2: 243, 1899.
9. Karsner, Howard T., and Dwyer, John E.: Studies in Infarction. IV. Experimental Bland Infarction of the Myocardium, Myocardial Regeneration and Cicatrization, *J. Med. Research* 34: 21, 1916.
10. Benson, Robert L., Hunter, Warren C., and Manlove, Charles H.: Spontaneous Rupture of the Heart, *Am. J. Path.* 9: 295, 1933.

COMBINED SYPHILITIC AORTITIS AND RHEUMATIC DISEASE OF THE HEART

REPORT OF FOUR CASES

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ALTHOUGH the combination of rheumatic disease of the heart with syphilis of the aorta is not extremely rare, an analysis of the available literature up to the present time discloses less than thirty case reports. A study of these cases indicates that approximately fourteen are quite definitely authenticated by both gross and microscopic observations. These include those reported by Sager and Sohval, Cabot, and Lisa and Chandlee. The genuineness of the remaining cases is open to question because no microscopic observations were reported. There are five cases in unavailable foreign literature which should be included in this group. Sager and Sohval,¹ reviewing the literature up to 1934, found seven reported cases of combined syphilitic and rheumatic disease of the heart and aorta. They presented three cases of their own, in which syphilitic aortitis was associated with both syphilitic and rheumatic infection of the aortic valve. These are the only ones in which this particular combination was present. In Cabot's² series of five cases, syphilitic aortitis was associated with rheumatic endocarditis of the various valves. Lisa and Chandlee³ reported six cases of syphilitic aortitis combined with rheumatic disease of either the myocardium or endocardium. In one of these, the syphilitic process involved the aortic valve.

The cases of Dumas and Brunat and Gallavardin and Gravier belong among those in which this combination has been less conclusively demonstrated. In Dumas and Brunat's⁴ case, syphilitic aortitis was associated with mitral stenosis and a chronic, cicatricial endocarditis. Although marked stenosis of the mitral valve was present, the lesions both in the aorta and mitral valve were considered to be syphilitic. Gallavardin and Gravier⁵ reported four cases in which syphilis of the aorta was combined with various rheumatic valvular lesions. In two cases, syphilitic aortitis was associated with rheumatic disease of two or more valves, while in the other two the syphilitic process was combined with rheumatic aortic stenosis. The microscopic findings were not reported in these cases.

Because of the relative frequency of syphilitic heart disease in this locality, an attempt was made to ascertain the incidence of this com-

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Received for publication June 1, 1939.

bination of diseases by a study of the autopsy material of the Vanderbilt Hospital. From 1925 to 1937, 1,841 autopsies were performed, and cardiovascular syphilis of all types was found in fifty-seven instances. There were also thirty-five cases of active rheumatic heart disease and thirteen cases of inactive rheumatic heart disease. Among these, there were four instances of syphilitic aortitis associated with either rheumatic endocarditis or rheumatic myocarditis.

CASE REPORTS

CASE 1 (V. H., No. 74001).—The patient was a 44-year-old white woman, who gave no history of rheumatic fever, chorea, or syphilis. She was admitted to the hospital Feb. 13, 1937, with lobar pneumonia of five days' duration. The past history revealed that she had first experienced exertional dyspnea fourteen years before admission, and that this was frequently associated with attacks of knifelike precordial pain which showed no tendency to radiate. In the preceding five years she had had dependent edema on several occasions. During the latter period, these symptoms had been fairly easily controlled with digitalis, and she had been able to go through a full-term, normal pregnancy without aggravation of her condition. However, nocturnal dyspnea had been present for two months prior to admission.

On admission, she displayed cyanosis of the lips and nail beds, with labored breathing, a cough which was productive of bloodtinged sputum, and a temperature of 102.2° F. There were evidences of consolidation of the right middle and lower lobes. The point of maximum intensity of the cardiac impulse was 9 cm. from the midsternal line in the fifth intercostal space. The right border of the heart was 3 cm. to the right of the midsternal line in the fifth intercostal space, and the retro-manubrial dullness measured 7 cm. in width. A rough, loud, systolic murmur was heard over the entire precordium, but with maximal intensity over the aortic area; it was transmitted over the neck vessels only moderately well. In the aortic region the murmur was loud, rough, and rumbling. The aortic second sound was absent, and there were no presystolic or diastolic murmurs. The pulse was small in volume and not well sustained. The blood pressure was 128/86 in both arms, and slightly higher in the legs. The lower border of the liver was felt one centimeter below the costal margin in the midclavicular line. There was no ascites, and the lower extremities were not edematous. The erythrocyte count on admission was 5.02 million, with 11.5 grams of hemoglobin. The leucocyte count was 21,950, 95 per cent of which were neutrophils. The urine showed nothing of note, and blood cultures were repeatedly sterile. The blood Wassermann reaction was strongly positive. Sputum cultures were positive for the type IV pneumococcus. A roentgenogram of the chest showed marked right auricular enlargement, a very prominent aorta, and complete consolidation of the upper lobe of the right lung. The patient grew worse progressively, and expired seven days after admission. Clinical diagnoses: (1) lobar pneumonia, upper lobe of right lung, due to type IV pneumococcus, (2) aneurysm of the ascending aorta, (3) rheumatic aortic stenosis, and (4) syphilis of the aorta.

Autopsy.—The heart weighed 300 grams. As it lay in situ, there was marked displacement of the right border caused by a tremendous dilatation of the first portion of the aorta. This was entirely to the right and slightly downward, so that it partially overlay the right auricle. The epicardium was not remarkable, there were no mural thrombi, and the chambers of the heart were not dilated. Myocardial scarring was absent, but the wall of the left ventricle measured 22 mm. in thickness, being slightly hypertrophied. The tricuspid and pulmonic valves appeared normal in all respects, and, aside from a slight fibrous thickening of the leaflets, the mitral

valve showed nothing remarkable. On section, the aortic ring was extremely firm. The cusps were distorted and fused into a solid, thick, projecting, shelflike structure, in the center of which was a narrow, "fish-mouthed" lumen. The attachments of the cusps were recognizable from the upper surface, and shallow sinuses were still present from which the coronary arteries arose as usual. The aortic ring measured 7 cm. in circumference, and the "fish-mouthed" lumen was $1\frac{1}{2}$ cm. in length by 3 mm. in width. The shelflike cusps were 4 to 5 mm. in thickness. On the undersurface were several minute, irregular depressions, and when a small probe was passed through the largest of these it emerged on the upper surface in a small nodule of fibrous tissue. Immediately beyond the aortic valve the aorta expanded abruptly into a large, fusiform, aneurysmal dilatation, measuring 6 by 8 cm. At the origin of the left carotid artery the aneurysm abruptly ceased, and a low, ridgelike projection marked its termination. There was no stenosis at this point. Within the aneurysm, the aortic wall was thin, irregular, and less elastic than elsewhere. There were fine longitudinal wrinkles just beyond the aortic valve.

Microscopically, the left ventricular muscle was hypertrophied, and there was a diffuse interstitial fibrosis which was largely perivascular. In rare instances there were perivascular groups of large and dark-staining cells which were suggestive, but not typical, of Aschoff bodies. The small arteries showed a moderate intimal fibrosis. A section through the aortic valve showed a diffuse, atrophic, and partially calcified fibrous thickening which had undergone hyalinization. Along the inner border, adjacent to the endocardium, there were innumerable fibroblasts and small round cells, as well as many thin-walled capillaries. This portion showed organization. Along the outer border of the leaflet, organization had occurred in the past, but coagulation necrosis was present. There were no areas of acute ulceration or vegetation, and the perivascular round-cell infiltration characteristic of a syphilitic process was absent. A section of the aorta through the ridge marking the termination of the aneurysm showed a fairly thick fibrous tissue proliferation which was partially hyalinized. The internal lamina was unusually thick and conspicuous, and the media appeared loose. There was some distortion of the elastic laminae, and a few small scars were present in the outer portion. The vasa vasorum showed little sclerosis, but the vessels along the junction of the adventitia and media were surrounded by round cells and plasma cells. Similar pictures were found elsewhere in the aorta. The anatomical diagnoses were: (1) Lobar pneumonia, right upper lobe, with extension to the right middle and lower lobes, (2) syphilitic aortitis with fusiform aneurysm of the arch and ascending aorta, (3) rheumatic aortic stenosis, inactive, with left ventricular hypertrophy, (4) acute fibrinopurulent pleurisy, and (5) parenchymatous degeneration of the liver and kidneys.

CASE 2 (V. H., No. 3155).—This patient, a 43-year-old negro, was admitted to the hospital Nov. 4, 1933, with acute pulmonary edema of one day's duration. He had had exertional dyspnea for two years, but had not been incapacitated. Edema of the lower extremities had been present occasionally, but this was apparently due to old varicosities and trophic ulcers of the feet. No history of rheumatic fever was obtained, but the patient had had a painless penile lesion twenty-six years before admission, for which he had received no treatment. In 1927, bilateral femoral sympathectomy was done in an attempt to heal the trophic ulcers of the feet. At that time, the blood and spinal fluid Wassermann reactions were strongly positive. His blood pressure at that time was 168/97, but there was no cardiac enlargement.

Physical examination revealed an acutely ill negro who was sitting propped up in bed; his breathing was difficult and labored, and he had a brassy cough which was productive of slightly bloodtinged sputum. There was edema of the lower extremities. The voice was hoarse and high-pitched. The cervical veins were distended even in the upright position, and did not collapse on inspiration. The retinal arteries

were tortuous, but there were no retinal hemorrhages or exudate. A tracheal tug was demonstrable. The pupils were unequal, irregular, and reacted sluggishly to light. Acute pulmonary edema was present. The point of maximum intensity of the apex beat was 14 cm. from the midsternal line in the sixth intercostal space. There were no shocks or thrills; the rhythm was normal and there were no diastolic murmurs. A short systolic murmur was heard over the aortic area and the pulmonic second sound was louder than the aortic second. The liver was not palpably enlarged, but ascites was present. A roentgenogram of the chest showed a large mass in the



Figs. 1 and 2, Case 1.—The heart and aorta, illustrating the aneurysm of the ascending aorta, and the marked thickening, distortion, and contraction of the aortic cusps.

Fig. 3, Case 1.—Photomicrograph of aortic valve. The diffuse scarring, with hyalinization and organization, is apparent. In the upper portion, a rather marked round-cell infiltration is seen.

upper mediastinum suggesting an aneurysm involving the innominate artery and aortic arch, with marked prominence of the aortic knuckle and dilatation of the descending aorta. Roentgenologically, the heart was enlarged to the left. Routine laboratory examinations, other than the roentgenogram and including the blood Wassermann reaction, showed nothing remarkable. The patient grew worse rapidly, and died Nov. 7, 1933, three days after admission. Clinical diagnoses: (1) Syphilitic aortitis with aneurysm of the arch of the aorta, (2) cardiac hypertrophy, dilatation, and insufficiency, (3) bronchopneumonia.

Autopsy.—The heart weighed 370 grams and was enlarged to the left. The epicardium was not remarkable. The myocardium was streaked with fat, and there were several small areas of scarring. The left ventricular wall was 1.5 cm. thick; the auricular wall was of normal thickness. The endocardium was smooth and glistening, but showed a few small, white scars. The tricuspid valve showed thickening and rolling of the edges of the valve leaflets, with a ballooning of the central portion. The chordae tendineae were prominently shortened and thickened. The pulmonic valve appeared normal grossly. The mitral valve was thickened and the edges rolled, so that some of the chordae tendineae, which were shortened and thickened, were attached to the upper surface of the valve leaflets. The aortic cusps sagged somewhat; there were thickening and scarring along the line of the attachment, and the commissures were markedly widened. The sinus of Valsalva was widely opened at the orifices of the coronary arteries, but the latter appeared normal grossly. There were small atheromatous plaques at the root of the aorta, but, as the arch was approached, there was an irregular wrinkling of the intimal surface with irregular plaques. Between the origin of the great vessels of the neck and the subclavian artery there was a large sacculated aneurysm containing laminated thrombi. The aneurysm extended upward into the neck and was intimately in contact with the trachea. The aorta was somewhat curved into the left pleural cavity below the aneurysm.

Microscopically, the epicardium appeared normal, while the myocardium exhibited edema and scarring of moderate degree. The myocardial fibers were hypertrophied, and brown atrophy of many of the fibers was present. Here and there were condensations of connective tissue suggestive of Aschoff bodies, but no typical cells were seen. The endocardium was edematous, and at one point there was a raised, fibrinous bundle in which blood cells and mononuclear cells were found. The coronary arteries showed intimal thickening of moderate degree. There was an irregularity in both the intima and media of the aorta caused by replacement of normal structures by fibrous tissue which in many instances was hyalinized. Scattered throughout the fibrous tissue were collections of fat, cholesterol crystals, and small collections of calcium. The scarring of the media almost replaced the normal structures. The vasa vasorum were thickened, and there was a perivascular infiltration of round cells and plasma cells which was very prominent. Anatomical diagnoses: (1) Syphilitic aortitis with aortic insufficiency and aneurysm of the arch of the aorta, (2) cardiac hypertrophy, dilatation, and insufficiency, (3) rheumatic mitral and tricuspid valvulitis, inactive, (4) acute passive congestion of the lungs and liver, (6) carcinoid of the cecum with metastasis to the liver, (7) thrombosis of the middle cerebral artery, and (8) perforating ulcers of the feet.

CASE 3 (V. H., No. 67804).—The patient, a 39-year-old negro, was first admitted to the hospital Nov. 24, 1934. He had been well until two years prior to admission, at which time he developed exertional dyspnea which had been progressive. Two months before entering the hospital he developed nocturnal dyspnea, and had to spend most of the time sitting upright in a chair. It was not until three days prior to admission that edema of the ankles appeared, and, with it, abdominal swelling became apparent. In addition, he had had periods of oliguria, alternating with nocturia and polyuria, for two months. He had had a gonorrheal infection at the age

of 24, which was followed in two months by a chancre. He received no treatment for syphilis at that time. The patient also gave a history of repeated attacks of sore throat which were frequently accompanied by pains in the knees and hips. These attacks became apparent after the age of 25. There was no other history suggestive of rheumatic infection. Ten years before admission to the hospital he was found to have a positive blood Wassermann reaction, and received an indefinite number of intravenous injections, after which his Wassermann reaction is supposed to have been negative.

Physical examination revealed a well-developed negro who exhibited extreme orthopnea, edema of the sacrum and lower extremities, and ascites. There was a marked carotid and substernal pulsation, the pulse was of the water-hammer type, and the blood pressure was 160/50 in both arms. The cardiac impulse was thrusting and heaving in the sixth intercostal space in the anterior axillary line. Suprasternal dullness was increased to the right, and the right border of the heart was 3 cm. beyond the midsternal line. At the apex there were a faint, systolic murmur, a diastolic murmur, and a rough presystolic rumble. As the left sternal border was approached the systolic murmur was still heard and the diastolic murmur became louder, reaching its maximum intensity in the fourth intercostal space on the left, at which point it had a musical, cooing-dove quality. The aortic second sound was replaced by this murmur. There was no tracheal tug, the pupils were equal, and the temperature of the face was the same on both sides. The pulses were synchronous. Scattered moist râles were heard at the bases of both lungs. The lower border of the liver could be percussed but not palpated. An old penile scar was present, together with hard, satellite, regional lymph nodes. The deep reflexes appeared normal. Laboratory examination revealed a normal blood cell count, an occasional erythrocyte in the urine, and a 40 per cent excretion of phenolsulphonephthalein in two hours. The blood Wassermann reaction was positive, as was the Kahn. An electrocardiogram showed left axis deviation. The spinal fluid Wassermann reaction was negative. A roentgenogram of the chest revealed marked cardiac enlargement, particularly of the left ventricle.

The patient was digitalized, fluids were restricted, and he was given diuretics. He improved and was discharged Dec. 8, 1934. Following his discharge he was able to carry on his normal activities with some restriction of his mode of living, and had no recurrence of nocturnal dyspnea until May 1, 1935, at which time he again developed acute pulmonary edema. The findings at this time were as before, but he did not respond to therapy, and expired May 3, 1935. Clinical diagnoses: (1) Syphilitic aortitis with aortic insufficiency, and (2) cardiac hypertrophy, dilatation, and insufficiency.

Autopsy.—The heart weighed 700 grams and was enlarged in all diameters, particularly to the left, and the left ventricle was hypertrophied. The myocardium showed an occasional small scar. Small, mural thrombi were present in the auricular appendages, but the endocardium appeared otherwise normal. The mitral, tricuspid, and pulmonary valves were thin, delicate, and competent, and measured 10 cm., 13 cm., and 7.5 cm. in circumference, respectively. The leaflets of the aortic valve were rolled, the edges were thickened, and there was a wide separation of the commissures. The edges of the thickened and shortened leaflets were irregular and projected upward to an apex in their middle, giving the appearance of a triangle, the base of which was at the attachment of the cusps to the aorta. The aortic ring was not appreciably dilated, but the contraction, separation, and distortion of the leaflets made an unquestionable insufficiency. The left auricle was hypertrophied, elongated, and slightly dilated. The right ventricle showed similar changes. There were wrinkling and puckering of the first portion of the ascending aorta and arch. Several raised, translucent, wrinkled plaques were present near the aortic ring; they ended rather abruptly just beyond the arch of the aorta, where the wrinkling and puckering were

most distinct. There was a slight aneurysmal dilatation of the arch of the aorta, without definite sacculation. The coronary arteries were patent throughout, showing only an occasional, small, sclerotic plaque, but the process in the aorta encroached somewhat upon the orifices.

Microscopically, the epicardium appeared normal, while the myocardium showed scarring and hypertrophy of the individual fibers. In the interstitial tissue of the left ventricle there were accumulations of cells with dark-staining nuclei and abundant purplish-pink cytoplasm. Some of these were multinucleated, and in a few places a giant cell was seen. There were plasma cells and round cells distributed about these large cells which were quite distinctive of Aschoff bodies. In the aorta, great accumulations of plasma cells and a few round cells were seen about the vessels in the adventitia and media. Many vessels had invaded the media, and there was scarring with a loss of elastic tissue and remarkable irregularity in all three layers of the aorta. The intima was thickened by fibrous tissue, and was separated from the media in some areas. Anatomical diagnoses: (1) Syphilitic aortitis with aortic insufficiency, (2) cardiac hypertrophy, dilatation, and insufficiency, (3) rheumatic myocarditis, acute, (4) acute intracapillary glomerular nephritis, (5) thrombosis of the right auricular appendages, (6) multiple infarcts of the lungs, (7) chronic passive congestion of viscera, and (8) aortic dilatation without aneurysm formation.

CASE 4 (V. H., No. 35936).—A 32-year-old negro was first seen Nov. 24, 1930, complaining of difficulty in hearing, tinnitus, vertigo, diplopia, and headache. These symptoms had been present for five months. In addition, he had noted exertional dyspnea for one year, accompanied by edema of the ankles. Under treatment by his local physician, the dyspnea and edema subsided. During the two months prior to his first admission he had experienced two attacks of unconsciousness without convulsions. Five years prior to the onset of his illness he had had a painless, penile lesion, associated with inguinal adenopathy. There was no history suggestive of rheumatic fever. The positive findings on the first admission were: general lymph node enlargement, hyperactive deep reflexes, normal air conduction as well as bone conduction, but definite diminution in auditory acuity for the spoken voice. The vision was 20/20, and there was no papilledema or optic atrophy. A soft, blowing, systolic murmur was audible at the apex, but there was no evidence of cardiac enlargement. The blood pressure was 126/88. The blood Wassermann reaction was positive, as was the spinal fluid Wassermann. The mastic reaction on the spinal fluid showed a curve of 5431000000. A diagnosis of central nervous system syphilis was made, and during the next two months he received six injections of bismuth and two injections of nearsphenamine (0.3 gm.).

On June 30, 1931, he was admitted to the hospital in coma. During the two weeks prior to admission he had had two convulsions, and, on the morning of admission, nine more. Coma had been present for six hours. The only positive findings on that admission were: rapid and deep respiration, hot and moist skin, contracted and unresponsive pupils, normal fundi, many rhonchi throughout the lungs, absent deep reflexes, and a blood pressure of 186/86. The blood sugar content was recorded as 347 mg. per cent, and the carbon-dioxide combining power of the blood as 17 vol. per cent. The urine was normal, and the nonprotein nitrogen content of the blood was 30 mg. per cent. A lumbar puncture revealed bloody spinal fluid, with an initial pressure of 110 mm. of water. The patient expired two hours after admission. Clinical diagnoses: (1) Diabetes mellitus, with coma, (2) syphilis of the central nervous system, type undetermined, (3) cerebral hemorrhage, site undetermined.

Autopsy.—The heart weighed 360 grams and was slightly enlarged. The epicardium and myocardium appeared normal grossly. The aortic cusps were thickened, particularly at their points of attachment, and there was a moderate sagging of the

cusps, but the commissures were not widened. Along the line of closure of the mitral valve there were numerous, small, firm, raised, translucent, pinkish-gray nodules, varying in length up to 3 mm. These were firmly attached to the superior surface of the valve and could not be torn away without tearing the cusp. They were not friable and did not show ulceration or other features of an acute bacterial vegetation. There was no rolling of the margin of the mitral cusps, and the



Fig. 4, Case 3.—Heart—hypertrophy and dilatation of left ventricle. The aortic cusps are rolled, thickened, and separated at their edges, and the commissures are widened. The first portion of the aorta shows well-defined wrinkled plaques.

Fig. 5, Case 3.—Aortic valve—classical aortic insufficiency, with syphilitic aortitis which stops rather abruptly just distal to the dilatation (beginning aneurysm) in the arch of the aorta. The syphilitic process encroaches upon the orifices of the coronaries to a slight degree.

Fig. 6, Case 3.—Photomicrograph of myocardium, showing a typical Aschoff body as observed in this case.

chordae tendineae were not abnormal. The remaining valves and endocardium appeared normal. The valve measurements were as follows: aortic, 7.5 cm.; pulmonic, 8 cm.; mitral, 9 cm.; tricuspid, 13 cm. At the base of the aorta there were numerous longitudinal wrinkles, as well as raised, yellowish plaques and pearly gray areas. The latter were the result of intimal thickenings, while the former were apparently associated with medial scarring. There was a slight dilatation of the posterior wall of the arch of the aorta. The lumina of most of the branches of the aorta were slightly constricted, and surrounded by radially arranged wrinkles. The intimal thickening increased toward the bifurcation, but the wrinkling disappeared in the upper portion of the thoracic aorta, ceasing very abruptly.

Microscopically, the epicardium appeared normal, but scattered throughout the myocardium were numerous small, fibrous scars. There were no areas of acute necrosis, but there were several areas of perivascular cellular infiltration. The predominant cell was relatively large, with clear, blue cytoplasm and a large vesicular nucleus. In these areas of cellular infiltration there were round cells and plasma cells in abundance, as well as an occasional polymorphonuclear leucocyte. These areas were typical Aschoff bodies. The intima of the aorta was thickened, and numerous slitlike spaces were seen within the intima. The media was the seat of profound changes characterized by numerous scars and many areas of perivascular round-cell infiltration. This same cellular infiltration was marked in the adventitia, and gave the characteristic picture of syphilitic involvement. Anatomical diagnoses: (1) Gumma of left frontal lobe, (2) syphilitic pachymeningitis and leptomenigitis, (3) syphilitic aortitis without aortic insufficiency, (4) syphilis of the aortic valve, and (5) rheumatic endocarditis, mitral valvulitis, and rheumatic myocarditis, acute.

DISCUSSION

The incidence of syphilitic aortitis, as determined by clinical and pathologic examination, has been variously estimated. Clawson and Bell,⁶ in studying several hundred autopsies in Minnesota, found that syphilitic aortitis occurred in 2.6 per cent of the necropsies; White⁷ has estimated that syphilitic aortitis represents not more than 4 per cent of all cardiovascular disease in New England. In a survey of 645 cases of organic heart disease in Tennessee, Laws⁸ found that syphilis was the etiologic agent in 7.9 per cent of the patients, and that rheumatic heart disease was present in 10.5 per cent of the cases. From a study of the autopsy material of various localities, White found that rheumatic heart disease with mitral stenosis occurred in from 0.08 to 3.89 per cent of all necropsies. The lower figure represents the incidence in New Orleans, and the higher figure that at a New England hospital. Of 1,841 autopsies performed at the Vanderbilt Hospital, syphilitic aortitis, both symptomatic and asymptomatic, was found in 3 per cent, while rheumatic heart disease of all types and grades occurred in 2.6 per cent. In this group, rheumatic heart disease was present in 7 per cent of the cases of syphilitic aortitis, and syphilitic aortitis was demonstrated in 8 per cent of the cases of rheumatic heart disease. The incidence of this combination has been estimated by others. Cowan and Rennie,⁹ in a clinical study of 104 patients with syphilis of the heart or aorta, found rheumatic involvement in 3.1 per cent of the cases. Reid,¹⁰ in

studying seventy-eight autopsy cases of cardiovascular syphilis, found rheumatic heart disease definitely associated in two cases, and probably also in a third. White states that this combination occurs in less than one per cent of all cases of cardiovascular disease. That our figures are higher than those previously reported may be due to the fact that syphilitic aortitis occurs more frequently in this locality than in those in which the above cases were observed.

The more frequent occurrence of the combined lesions among the negroes in our group is probably of no particular consequence, for forty-one of the forty-seven patients with syphilitic aortitis were negroes. Twelve of the thirty-five patients showing rheumatic heart disease were negroes.

Various authors, in discussing the combined lesions, have suggested that one predisposed the heart to a subsequent infection by the other. Lisa and Chandlee thought that the syphilitic process might have rendered easier the secondary invasion by the rheumatic infection in those cases in which the rheumatic infection occurred after the syphilitic lesion. Warthin¹¹ believed that latent syphilis in a young person predisposed him to secondary bacterial endocarditis, and Coombs¹² also thought that a syphilitic valve was disposed to secondary infection. Friedlander¹³ stressed the frequency of myocarditis in congenital syphilis, stating that syphilitic myocardial damage may often be the only manifestation of congenital syphilis. This is of interest, inasmuch as in two of our cases, in which the rheumatic infection almost certainly followed the syphilitic lesion, acute rheumatic myocarditis was present in association with syphilitic aortitis. According to Lisa and Chandlee, the syphilitic process may cause an exacerbation of a low-grade, asymptomatic, rheumatic heart disease of sufficient intensity to result in its passage into a clinical entity. However, there is, as yet, no definite evidence of any connection between the two diseases, and our series is too small to permit conclusions to be drawn.

In our series, the duration of congestive failure after the initial break in compensation varied from fourteen years to eighteen months. In Case 1, the patient lived fourteen years after the onset of exertional dyspnea; the rheumatic aortic stenosis was apparently the initial lesion and assumed the major role. The syphilitic aortitis and aneurysm of the aorta were secondary. The course in this case corresponded fairly closely with that of uncomplicated rheumatic aortic stenosis. However, in the three remaining cases, the duration of congestive failure averaged twenty-two months. This figure is much lower than the average usually encountered in pure rheumatic heart disease, and slightly higher than in cases of syphilitic heart disease. In this latter group the rheumatic lesions were of secondary interest and apparently remained silent, while the syphilitic process predominated and assumed its usual manifesta-

tions. The average duration of life after the onset of congestive failure was fourteen months in forty cases of syphilitic aortitis observed at the Vanderbilt Hospital.

Clinically, it is often impossible to establish the diagnosis of combined rheumatic heart disease and syphilitic aortitis. In three cases in this series this was true, and the diagnosis was made only at autopsy. However, in Case 1, the presence of aortic stenosis associated with clinical and roentgenologic evidence of aneurysm of the aorta and a positive blood Wassermann reaction made it possible to establish the correct diagnosis. This particular combination of the two lesions, and cases of aneurysm of the aorta with mitral stenosis and without aortic insufficiency are probably the only two combinations in which the diagnosis can be made with certainty clinically. One may suspect the coexistence of the two diseases in cases in which the following clinical features are present: (1) aneurysm of the aorta together with aortic insufficiency and a presystolic murmur, (2) mitral stenosis with aortic insufficiency in a case in which the presystolic murmur appeared prior to the diastolic murmur and in which there are clinical evidences of syphilis, and (3) aneurysm of the aorta with a diastolic murmur in a case in which there is a good history of previous rheumatic infection. There are undoubtedly other combinations which might be detected, but they are less certain than the above. In cases of obscure and bizarre cardiovascular disease in which there are a history of previous rheumatic fever and clinical evidences of syphilis, the possibility should be suspected and excluded. This is especially true if the course of the disease is much shorter than is ordinarily the case with uncomplicated rheumatic heart disease.

The difficulties encountered in making a diagnosis of the combined lesions is well illustrated by the following case. This patient, a 44-year-old white man, had acute, migrating polyarthritides in 1929, and sometime later was found to have a systolic murmur at the apex which had not been present at the first examination. In 1935, he contracted syphilis. In June, 1937, he developed exertional dyspnea which was rapidly progressive. One year later, examination revealed extreme cardiac hypertrophy and dilatation, an early systolic thrill limited to the aortic area, and a loud, high-pitched, rough, systolic murmur, followed by a softer diastolic murmur, in the second left intercostal space. As the apex was approached these murmurs were replaced by a loud systolic murmur, which, in turn, was followed by a late diastolic rumble. There was gallop rhythm at the apex. The blood pressure was 140/78, and the usual signs of cardiac insufficiency were present. The blood and spinal fluid Wassermann reactions were positive. This patient expired one year after the onset of congestive failure. At necropsy, he was found to have rheumatic endocarditis of the mitral and tricuspid valves with mitral stenosis and tricuspid insufficiency, healed bacterial endo-

carditis of the aortic valve which was superimposed upon what appeared to be a very early syphilitic aortitis with valvular involvement and also rheumatic valvulitis, and an inactive rheumatic myocarditis. The aortic valve was stenotic and insufficient, and a very extensive and destructive lesion was present. Two of the aortic cusps were perforated, and, grossly, the third resembled the typical syphilitic valve. Here, then, was a case in which there were both a history of rheumatic fever and syphilis with multiple cardiac signs and a very rapidly fatal termination. One observer believed that the patient had syphilitic aortitis with aortic insufficiency, while another made a diagnosis of rheumatic aortic and mitral stenosis with insufficiency. The possibility of combined syphilitic and rheumatic lesions was considered. This case is not listed with the other four in our series because, although the man probably had syphilis of the aortic valve in association with the rheumatic infection and the healed bacterial endocarditis, the nature of the pathologic changes was not indisputable.

SUMMARY

1. The clinical and pathologic findings in four cases of combined syphilitic aortitis and rheumatic heart disease are reported and discussed.
2. Contrary to the previously accepted idea that rheumatic heart disease occurs rarely in the southern states, our figures show that, clinically, rheumatic heart disease occurs more frequently in this locality than syphilitic aortitis, and almost as frequently at autopsy.
3. From the evidence now available, one can draw no conclusions concerning the possible interrelationship of these two forms of heart disease.

REFERENCES

1. Sager, Robert, and Solval, Arthur: Combined Syphilitic and Rheumatic Disease of the Aortic Valve, *Arch. Path.* 17: 729, 1934.
2. Cabot, Richard: *New England J. Med.* 201: 177, 1929; *New England J. Med.* 203: 1163, 1930; *New England J. Med.* 206: 401, 1932; *New England J. Med.* 206: 689, 1931; *New England J. Med.* 209: 555, 1933.
(The above were cases used in the clinical-pathologic conference at Harvard.)
3. Lisa, James, and Chandlee, Gertrude: The Heart and Great Vessels in Combined Syphilitic and Rheumatic Infection, *Arch. Int. Med.* 54: 952, 1934.
4. Dumas, A., et Brunat: Aortite histologiquement Syphilitique, Endocardite Cicatricielle avec retrecissement de la Valvule Mitrale, *Lyon Med.* 139: 577, 1927.
5. Gallavardin, M., and Gravier, L.: Des Modes de Coexistence d'une Aortite Syphilitique avec une Endocardite Aigue ou Chronique Non-syphilitique, *Lyon Med.* 145: 541, 1930 (cases 3, 4, 5, and 6).
6. Clawson, B. M., and Bell, E. J.: Heart in Syphilitic Aortitis, *Arch. Path.* 4: 922, 1927.
7. White, Paul: *Heart Disease*, Ed. 2, Macmillan.
8. Laws, Clarence: The Etiology of Heart Disease in Whites and Negroes in Tennessee, *AM. HEART J.* 8: 608, 1933.
9. Cowan, J., and Rennie, J. K.: Syphilis of the Heart, *Brit. M. J.* 2: 184, 1921.
10. Reid, Wm.: Diagnosis of Cardiovascular Syphilis, Analysis of Clinical and Post-mortem Findings, *AM. HEART J.* 6: 91, 1930.
11. Warthin: Syphilitic Myocarditis, *Lancet*, August 10, 1929.
12. Coombs, C. F.: Syphilis of the Heart and Great Vessels, *Lancet* 2: 227, 1930.
13. Friedlander, A.: Myocardial Degeneration in Congenital Syphilis, *Trans. Am. Ped. Soc.* 33: 308, 1921.

THE EARLIEST CORRELATION OF CLINICAL AND EXPERIMENTAL AURICULAR FIBRILLATION

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FIBRILLARY activity of cardiac muscle was first demonstrated by Hoffa and Ludwig,¹ in 1850, as a result of their attempt to produce tetanic contractions in the ventricles of various cold-blooded animals and mammals by direct faradization. The same phenomenon was produced by Einbrodt,² in 1860, and later by Vulpian,³ who also observed that a similar, but generally more transient, condition could be produced in the auricle of the dog. However, the clinical occurrence and importance of auricular fibrillation were overlooked for at least twenty-five years, and the condition was regarded primarily as a laboratory curiosity, being frequently produced by direct faradization of the heart and the administration of various toxic and pharmacologic agents. It is true that irregularities of the pulse in man were observed and recorded by Marey⁴ as early as 1863, and later by Riegel,⁵ Sommerbrodt,⁶ Janowski,⁷ and numerous other clinicians. These irregularities were given a variety of names, such as the "mitral pulse," delirium cordis, pulsus irregularis perpetuus, and the absolutely irregular pulse. However, they were neither adequately recognized as definite clinical entities, nor correlated with those experimentally observed in animals, such as auricular fibrillation. Indeed, it was not until 1903 that Hering⁸ definitely established the fact that the absolutely irregular pulse is a definite clinical entity. With the introduction of the electrocardiograph, Lewis⁹ and Rothberger and Winterberg¹⁰ ultimately proved that the majority of these irregularities observed in man were one and the same, and were the clinical counterpart of the experimental auricular fibrillation observed in animals.

The correlation between the clinical and laboratory observations was suggested, however, prior to the publication of the papers of Lewis and Rothberger and Winterberg. This earlier correlation was an outgrowth of the investigations of Arthur Cushny, undertaken while he was professor of Materia Medica and Therapeutics in the Medical School of the University of Michigan, at Ann Arbor. Cushny¹¹ states that he had been interested in cardiac irregularities as early as 1890. He was familiar with auricular fibrillation as produced in animals, both by direct faradization of the heart and by the administration of various drugs, such as digitalis, and he had frequently observed the condition in his labora-

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Received for publication June 2, 1939.

tory. This led him to wonder about the nature of the various pulse irregularities observed in man. In collaboration with George Dock, who was at that time professor of Medicine at Ann Arbor, he was able to study such irregularities in man by means of the Jacquet sphygmograph. With this instrument he recorded the radial pulse in patients with all of the types of irregularities of the heart which he had observed in his laboratory animals. In 1899 he published¹¹ the results of this work, and in this paper he pointed out the similarity of the clinical sphygmogram in cases of delirium cordis and that obtained from dogs during auricular fibrillation, and suggested that the two conditions might be identical. Previous to this, no writer had even faintly hinted at such an idea, but, nevertheless, the suggestion was entirely overlooked at the time.

In 1906, and again in 1907, Cushny,^{12, 13} in collaboration with Edmunds, published and compared pulse tracings from a patient with delirium cordis and those from dogs with experimentally produced auricular fibrillation. With these more complete data, the suggestion regarding the identity of the two conditions was reiterated. This suggestion was first recognized and discussed by Wenekebach,¹⁴ later by Lewis,⁹ and more recently by Garrey.¹⁵ In 1912, Lewis¹⁶ pointed out that his remembrance of the original suggestion and paper by Cushny and Edmunds¹² finally led him to compare more closely, and finally to correlate, the electrocardiograms from animals with auricular fibrillation with those obtained from patients with an absolutely irregular pulse. In general, however, more recent writers (e.g., White¹⁷) appear only vaguely aware of this contribution, and have given it scant notice. Because this was the first correlation of the laboratory and clinical observations, because the existence of this correlation is not more generally known, and, finally, because there is an important and historically interesting phase of this story that is entirely unknown, a presentation of the complete history of this contribution seems justified.

On Dec. 23, 1901, Mrs. H. H., a 64-year-old widow, entered the University Hospital, in Ann Arbor, complaining chiefly of an ovarian fibroid. She was sent to the Gynecology Service of Dr. Reuben Peterson and was successfully operated upon. At this time Dr. Charles Edmunds was an intern on this service, and during his routine examination of the patient he observed a paroxysmal irregularity of the pulse. He had been interested in cardiac irregularities and had previously discussed with Cushny the latter's observation, made in 1899. This interest led him to make tracings of this patient's radial pulse by means of the Jacquet sphygmograph. The resemblance of these tracings to those he had seen Cushny make on dogs with auricular fibrillation aroused his curiosity, and he had Cushny examine the patient. The original hospital records of this patient, which are reproduced here in part (Figs. 1, 2, and 3), substantiate these statements. Fig. 3 is a portion of the daily

record of the patient, indicating the clinical observation of the paroxysmal irregularity of the pulse, and showing that the patient was examined by Cushny on Dec. 28, 1901, the day the pulse tracings were made. It is of interest to note the comment that the patient herself had noticed the irregularity previously. The pulse tracings that were made have been reproduced from the originals (Figs. 4 and 5). Cushny compared these tracings with those secured from dogs with auricular fibrillation (Fig. 6). He believed that the striking resemblance constituted excellent evidence in favor of his original suggestion.

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DEPARTMENT OF GYNECOLOGY.

PAGE 1

HOSPITAL NO 988

CASE NO 86

Name H. M. H.

Address Lansing Mich

Occupation Housewife

Age 64. Nationality American

Race White

Married 5 yrs

Referred by Dr. H. H. H.

Address Unadilla Mich

Admitted Dec 23, 1901

Family History - Grandfather had a cancer on hand, a brother cancer on hand. Both dying from this cause.

Personal History - About 25 yrs ago had an attack, had a severe backache in the lumbar region. Very painful to pressure, something in back and on the chest of stern. After about 6 wks after some attack of vomiting, broke and discharged into the rectum, very foul smelling. I had fevers, and discharged through the rectum 11-15 times. I had not been out for a while, certainly extended. Was sick with it nearly 2 yrs. The point of remission, however, seemed to be near the lumbar point.

Age of appearance 13

Date of last period 1909.

Number of years married 5

Number of years widow 5

Menstrual

Regularity Unusually

Duration 3-4 days

Amount

Color

Clots Some

Pain Great deal

Kind

When Back

Married

Labor at duration

Instruments

Abortions Date 1/2 0

month 1/2 0

Leucorrhoea

Duration Several yrs.

Amount

Character

Odor

Puerperal history 0

Fig. 1.—The first page of the original hospital record of Mrs. H. H., a 64-year-old widow, who entered the University Hospital Dec. 23, 1901.

On March 12, 1902, Edmunds presented this material at the regular meeting of the Ann Arbor Medical Club, and in his discussion of the paper Cushny reiterated his belief in the identity of the clinically observed arrhythmia and experimental auricular fibrillation. He pointed out that in both conditions (compare Figs. 4 or 5 and 6) there was not only an irregularity with respect to sequence of pulses, but also in their amplitude. Thus, for example, in the upper tracing of Fig. 5, if one considers the downstrokes after any of the first few smooth upstrokes, one sees many small pulses which are irregular in sequence and amplitude. A comparison with the upper tracing of Fig. 6, which was taken from a dog during experimental auricular fibrillation, shows the same thing.

University of Michigan

UNIVERSITY HOSPITAL.

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DEPARTMENT OF GYNECOLOGY.

NAME. H.

Mrs H

CASE NO. 86

PAGE 11

HOSPITAL NO. 978

Physical examination by Dr. Edmunds:

The abdomen is filled with a hard smooth solid tumor. The mass is partially divided into two lobes by a longitudinal sulcus which reaches from about 5" above pubes to 2" above umbilicus and 1/2" to right of the latter. Just above pubes the lobes are fused together into one solid mass. The lobe on left is larger than that on right and reaches upwards to border of ribs. Laterally it extends to within 1 1/2" of anterior superior spines. The right lobe extends well over the right anterior superior spine but its upper border is about 1/4" from border of ribs. There is complete flatness over area occupied by tumor which is somewhat movable and non-sensitive.

Vaginal examination

A small cervix can be made out ^{pointing to left} ~~in same position~~ two hard smooth masses about the size of egg half walnut can be felt, each projecting from cervix at supravaginal junction. The uterus measures 2 1/2" and cervix to be directly continuous with tumor mass. When latter is moved the cervix moves also. The tumor can be felt projecting into pelvis on all sides of uterus. Circumference of abdomen 1" below umbilicus = 37 1/2" between anterior superior spines 1" below umbilicus = 16 1/2"

Fig. 2.—The second page of the hospital record of Mrs. H., showing the physical examination as recorded by Dr. Edmunds.

DEC 25 1901 Still unimproved slightly. Stomach moved. Pulse more and irregular.

Her 29. Exam by Dr. Cushman. Halobion 90% prescribed for. Pulse very irregular. Patient has noticed emetion before.

Her 30. 3 weeks well. Ordered beef steak.

Jan 1 1902 Pulse very irregular Halobion discontinued two days ago because stomach was upset.

Jan 2 1902 3 weeks well. 13 stitches removed by Dr. Burr. Taking food well. Pulse more regular. The upper part of wound some what gaping. No infection. Still has private nurse.

Jan 3 1902 3 weeks well. Pulse regular. Moved into ward yesterday.

Fig. 3.—A portion of the daily progress notes kept on the patient. Note the examination by Dr. Cushman on December 29.

Unfortunately, the observations presented to the Ann Arbor Medical Club received practically no notice. The proceedings of this organization were irregularly recorded in the *Physician and Surgeon*, a medical journal published in Ann Arbor for several years, but the proceedings of this particular meeting were omitted. The result was that the paper which was presented in 1902 remained buried in obscurity. However, it has been possible to locate the original records of the Ann Arbor Medical

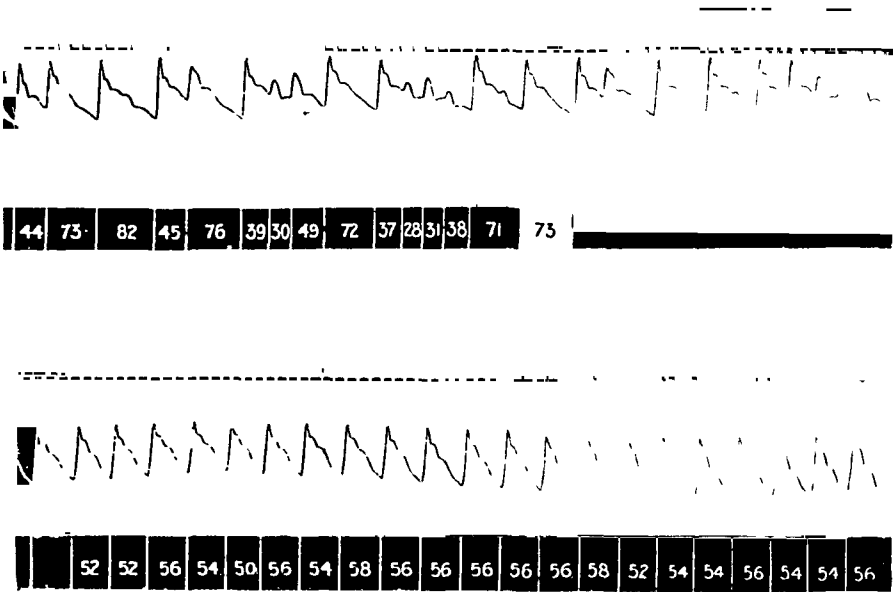


Fig. 4.—Pulse tracings made by means of the Jacquet sphygmograph on December 28. Upper tracing was made at 1:45 P.M., lower tracing at 2:45 P.M.

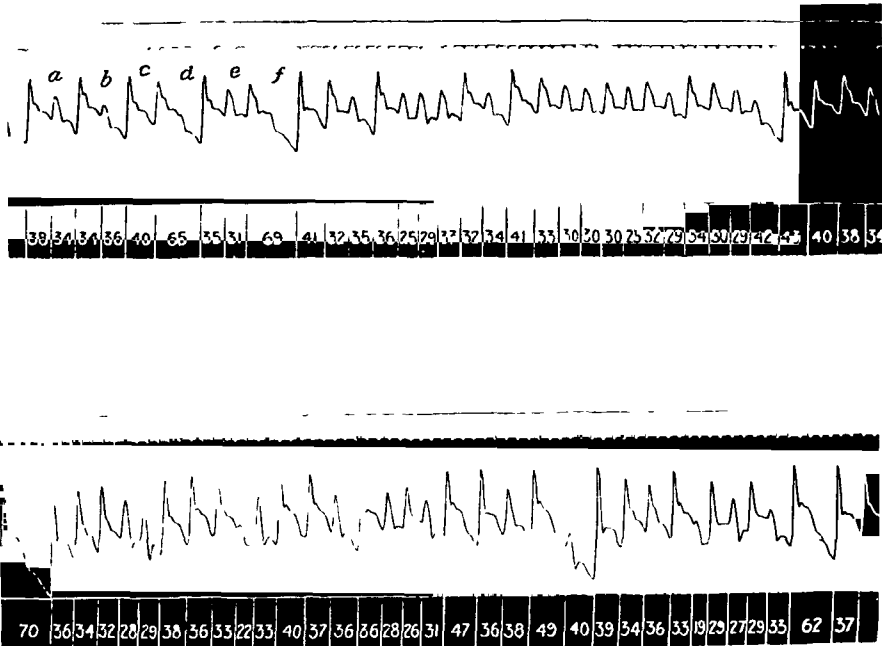


Fig. 5.—Further pulse tracings made on December 28. Upper tracing was made at 3:45 P.M., lower tracing at 4:45 P.M.

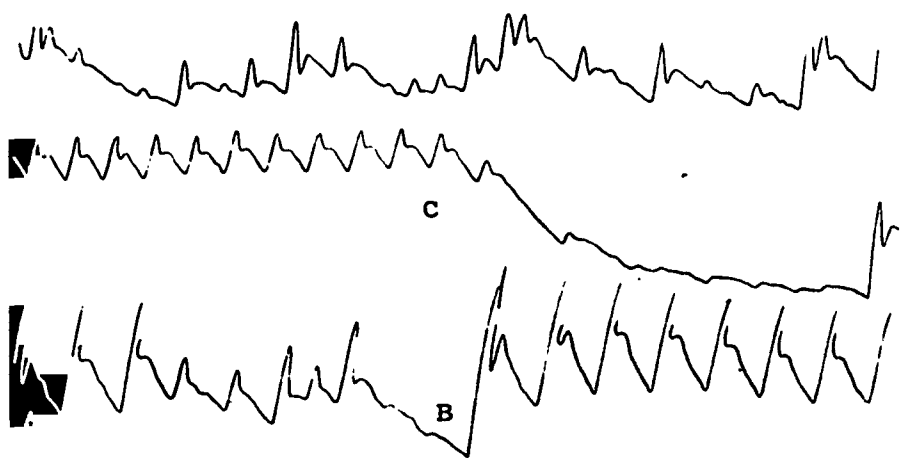


Fig. 6.—Tracings from carotid of dog made by means of Hürthle's tonometer. Uppermost tracing made during prolonged fibrillation. In middle tracing fibrillation was induced at C. In lowermost tracing there was imperfect fibrillation from A to B, no fibrillation after B.

The following papers were
 read in the program for
 the evening:
 The Diagnostic Use of Tuberculin
 Doctor George, Doct.
 "A Study of the Liver in Doct.
 Dr. Warden of Washington.
 "A Study of Tuberculin in
 a Case of Cardiac
 Hypertrophy, Doctor C. W.
 Edmunds.
 Doctor Foster's paper which
 was illustrated by a
 large number of charts
 was discussed by
 Doctor Vaughan, Fisher,
 Good and Peterson.
 Doctor Warden's paper was
 commented upon by
 Doctor August Vaughan;
 and Doctor Edmunds
 paper, which was also
 accompanied by chart
 illustrations was
 discussed by Doctor Oakley
 (Albany).
 John Hollenbecker
 Secretary

Fig. 7.—Page from record of Ann Arbor Medical Club, March 12, 1902, showing the papers given. Note the third paper read, and the notation at the end regarding the discussion by Dr. Cushny.

Club which were kept by the secretary. A portion is reproduced here (Fig. 7), and confirms the facts as given. Thus it will be seen (Fig. 7) that a meeting was held March 12, 1902, and that, in addition to several other papers, Dr. Charles Edmunds presented one, entitled "A Study of Pulse Tracings From a Case of Cardiac Arrhythmia." In addition, the notation is made that Dr. Cushny discussed the paper and the accompanying pulse tracings that were presented. For a knowledge of what was said in the course of the discussion the author is indebted to the excellent memory of Dr. Edmunds. In addition, we have the later statement of Cushny¹⁸ that he had reached the conclusions stated here as early as 1901.

We thus have evidence of the original and definite correlation of delirium cordis in man with experimental auricular fibrillation. It should be emphasized that this was accomplished seven years prior to the presentation of the final proof by Lewis and Rothberger and Winterberg that the two conditions are identical. The further history of this patient is of interest. As has been pointed out, the case, including the pulse tracings and conclusions, was finally reported in 1906, and again in 1907. The 1906 report¹² was rather obscure and passed unnoticed. Fox¹⁹ further studied and reviewed this case. The patient was seen occasionally at the University Hospital for several years. When examined for the last time, in 1909, her cardiac irregularity had become permanent, and eventually she showed all the evidences of the cardiac failure which finally led to her death.

The author wishes to acknowledge gratefully the kind interest and valuable help of Dr. Arthur C. Curtis and Dr. Charles W. Edmunds in the preparation of this paper.

REFERENCES

1. Hoffa, M., and Ludwig, E.: Einige neue Versuche über Herzbewegung. *Ztschr. f. rat. Med.* 9: 107, 1850.
2. Einbrodt: Über Herzreizung und ihr Verhältniss zum Blutdruck. *Sitzungsber. d. k. Akad. d. Wissensch. Math.-naturw. Cl., Wien* 38: 345, 1860.
3. Vulpian, A.: Sur les effets de la faradization des ventricules du coeur chez le chien. *Compt. rend. Soc. de biol.*, 1: 6.s., 394, 1875; also, *Gaz. méd. de Paris*, 4, 4. s., 16, 1875; also, *Arch. de physiol. norm. et path.*, Paris, 1, 2.s., 975, 1875.
4. Marey, Étienne J.: *Physiologie médicale de la circulation du sang, basée sur l'étude graphique des mouvements du coeur et du pouls artériel, avec application aux maladies de l'appareil circulatoire.* P. 568, Paris, 1863, A. Delahaye.
5. Riegel, F.: Über Arrhythmie des Herzens. *Samml. klin. Vorträge (Volkmann), n.F.*, No. 227 (*Inn. Med.*, 68), 1309, 1898.
6. Sommerbrodt, J.: Über Allorhythmie und Arrhythmie des Herzens und deren Ursachen. *Deutsches Arch. f. klin. Med.* 19: 392, 1877.
7. Janowski, W.: Über die diagnostische und prognostische Bedeutung der exakten Pulsuntersuchung. *Samml. klin. Vorträge (Volkmann), n.F.*, No. 192 (*Inn. Med.*, 57), 975, 1897.
8. Hering, H. E.: Analyse des Pulsus irregularis perpetuus. *Prag. med. Wehnschr.* 28: 377, 1903.
9. Lewis, T.: Auricular Fibrillation; a Common Clinical Condition, *Brit. M. J.* 2: 1528, 1909; *Heart* 1: 306, 1909-10.
10. Rothberger, G., and Winterberg, A.: Vorhofflimmern und Arrhythmia perpetua, *Wien. klin. Wehnschr.* 22: 839, 1909.
11. Cushny, A.: On the Interpretation of Pulse-Tracings, *J. Exper. Med.* 4: 327, 1899.

12. Cushny, A., and Edmunds, C. W.: Paroxysmal Irregularity of the Heart and Auricular Fibrillation. *Aberdeen University Studies (Bulloch)* 21: 95, 1906.
13. Cushny, A. R., and Edmunds, C. W.: Paroxysmal Irregularity of the Heart and Auricular Fibrillation. *Am. J. M. Sc.* 133: 66, 1907.
14. Wennekebach, K. F.: Beiträge zur Kenntnis der menschlichen Herztätigkeit. *Arch. f. Anat. u. Physiol., Physiol. Abt.* p. 1, 1907.
15. Garrey, W. E.: Auricular Fibrillation, *Physiol. Rev.* 4: 215, 1924.
16. Lewis, T.: A Lecture on the Evidences of Auricular Fibrillation Treated Historically, *Brit. M. J.* 1: 57, 1912.
17. White, P. D.: *Heart Disease*, P. 744, New York, Ed. 2, 1937, The Macmillan Co.
18. Cushny, A. R.: Irregularities of the Heart and Auricular Fibrillation, *Am. J. M. Sc.* 141: S26, 1911.
19. Fox, G. H.: The Clinical Significance of Transitory Delirium Cordis, *Am. J. M. Sc.* 140: S15, 1910.

THE ELECTROCARDIOGRAM IN THE AGED

A STUDY OF 100 MEN AND WOMEN OVER THE AGE OF 70 WITH APPARENTLY NORMAL HEARTS

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IN TREATING a large number of aged persons in whom no cardiac disease is apparent, one is struck by the unexpected frequency with which electrocardiographic abnormalities are found. Despite careful history and physical examination, which give no indications of heart disease, electrocardiographic study in many instances reveals marked changes. The present study was made to determine the number of supposedly normal people in the upper age groups whose electrocardiograms show definite changes—changes that are commonly accepted as indicative of a diseased heart. A follow-up study with autopsy material is not included in this paper. Willius¹ reviewed the electrocardiograms of 700 people over the age of 74 years. Fifty-five per cent had abnormal tracings. What proportion of his group had clinically normal hearts was not stated. Gelman and Brown² studied the electrocardiograms of 121 normal children between the ages of 12 and 14, as compared with a group of 60 “normals” over the age of 61. Of the latter group, the records showed a negative T_1 and T_2 in 10 per cent, and depression of S- T_1 and S- T_2 in 36 per cent (degree not stated). None of these changes occurred in the children. Their definition of “normal” was based on the absence of clinical manifestations of heart disease.

MATERIAL

The patients studied were chosen from the general medical clinic of the University of Minnesota. The group included only persons 71 years of age, or over, in whom no disease of the cardiovascular-renal system was evident, with the exception of the usual changes in the palpable vessels. Those selected fulfilled the following requirements: (1) A painstaking history elicited no symptoms of cardiovascular-renal disease; (2) the sensorium was clear, so that an accurate history could be obtained; (3) the blood pressure was not over 90 diastolic or 170 systolic; (4) physical examination showed no cardiac enlargement or diastolic murmur; (5) there was no evidence of syphilis, diabetes mellitus, or cerebral or acute infectious disease; (6) examination of the urine showed no evidence of renal disease; (7) chronic bronchitis, emphysema, and bronchial asthma were absent. All histories were taken, and physical examinations made, by the writer. Particular emphasis was placed on the history. The subjects selected were able to perform such tasks as walking two miles, washing clothes, running a household,

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Received for publication June 14, 1939.

or performing regular duties of a manual nature without dyspnea or a sense of tightness in the chest. None had attacks of nocturnal dyspnea.

They were further questioned concerning severe attacks of painless weakness, with sweating, which might suggest acute coronary occlusion. All these people stated that they were leading an active life, but at a slowed tempo. Prostatic symptoms, carcinoma of the skin, chronic arthritis, and diseases of the eye were the presenting complaints in over 90 per cent of the cases. Sixty-four were men, and 36 were women. Eighty-two were in the eighth decade, sixteen in the ninth, and two in the tenth.

The criteria of an abnormal electrocardiogram were: R-T or S-T segment elevated or depressed more than 1 mm. in relation to the isoelectric line; T waves diphasic, isoelectric, or inverted in Lead I or II, or both; QRS interval longer than 0.10 second; presence of a Pardee Q_s. Auricular fibrillation, P-wave changes, and alterations of the P-R interval were not included.

RESULTS

Twenty-six of these patients, sixteen men and ten women, showed an abnormal electrocardiogram, according to the above criteria. These abnormalities are summarized in Table I. The incidence in the various age groups will be seen in Table II. The sex incidence is essentially the same as that in the entire group. In the remaining seventy-four cases, premature beats were present in twenty-three, left axis deviation in fifty-nine, and right axis deviation in two.

COMMENT

It is well known that changes in the ventricular complex are not always identified with a diseased myocardium; also, myocardial disease is sometimes found when the tracing is normal. However, the electrocardiogram is invariably altered in the presence of severe heart muscle damage.³ Consequently, the pronounced changes found in 26 per cent of our patients should be interpreted with the fact in mind that in rare instances the electrocardiogram is at variance with demonstrable heart lesions.

The frequency with which myocardial changes remain symptomless is well appreciated. In a series of articles devoted to the pathology of old age, Aschoff⁴ cites the frequency of sudden death from coronary disease in old people who had boasted, "My heart is the healthiest organ in my body." Aschoff further states that the usual changes in senility, namely, brown pigmentation, increase in connective tissue, and fat deposits in the conduction system, are without effect on the electrocardiogram. Nathanson⁵ reported a series of cases of coronary sclerosis in 37 per cent of which there was normal blood pressure, the heart was normal in size, and there was no cardiac insufficiency. Nathanson did not indicate how many of this group gave a history suggestive of coronary disease.

The frequency of asymptomatic coronary disease in the aged was pointed out by Gorham and Martin,⁶ whose study revealed an increase

TABLE I

DETAILS OF THE 26 CASES IN WHICH THE ELECTROCARDIOGRAMS WERE ABNORMAL

CASE NO.	AGE	SEX	ADMISSION DIAGNOSIS	ELECTROCARDIOGRAPHIC CHANGES
8	77	F	Cataract	T ₁ isoelectric. Low voltage—L. axis deviation.
9	73	M	Carcinoma of the face	T ₁ and T ₂ inverted. L. axis deviation.
2	72	M	Bladder stone	T ₁ isoelectric. L. axis deviation.
4	80	M	Tumor of eyelid	QRS 0.14. QRS notched and slurred. L. axis deviation.
18	71	M	Tumor of face	QRS 0.14. QRS notched and slurred. Low voltage.
19	81	F	Cataract	QRS 0.12. L. axis deviation. Pardee Q ₃ .
24	74	M	Inguinal hernia	T ₁ negative. Auricular fibrillation. L. axis deviation.
26	72	F	Chronic hyp. arthritis	S-T ₁ and S-T ₂ depressed. T ₁ isoelectric.
32	75	F	Chronic hyp. arthritis	S-T ₁ depressed. L. axis deviation. T ₁ isoelectric.
35	76	F	Cataract	T ₁ isoelectric. QRS 0.12.
36	76	M	Benign hypertrophy prostate	QRS 0.14. L. axis deviation.
37	77	M	Ca. stomach	T ₁ isoelectric. L. axis deviation. Auricular fibrillation.
44	78	M	Benign hypertrophy prostate	QRS 0.12. Low voltage.
51	75	F	Carcinoma of the face	QRS 0.14. Rt. axis deviation.
53	71	F	Glaucoma	S-T ₁ and S-T ₂ depressed. T ₁ and T ₂ diphasic. L. axis deviation.
59	79	M	Chronic dermatitis	Right bundle branch block.
64	73	M	Benign hypertrophy prostate	S-T ₁ depressed. T ₁ inverted. L. axis deviation.
66	87	F	Cataract	QRS 0.12. S-T ₁ elevated. L. axis deviation.
72	91	F	Cataract	T ₂ and T ₃ inverted. Rt. axis deviation.
73	71	M	Carcinoma of the face	S-T ₁ and S-T ₂ depressed. L. axis deviation.
78	71	F	Cataract	S-T ₁ and S-T ₂ depressed. L. axis deviation.
84	81	M	Benign hypertrophy prostate	Lt. bundle branch block.
86	76	M	Benign hypertrophy prostate	T ₁ inverted. L. axis deviation.
87	85	M	Cataract	QRS 0.14. QRS notched and slurred.
91	71	M	Carcinoma of lip	Isoelectric T ₁ . Inverted T ₂ . Auricular fibrillation.
93	76	M	Benign hypertrophy prostate	T ₁ isoelectric. S-T ₁ depressed. Rt. axis deviation.

TABLE II

AGE DISTRIBUTION, BY DECADES, OF SUBJECTS WITH ABNORMAL ELECTROCARDIOGRAMS

AGES	CASES	ELECTROCARDIOGRAPHIC CHANGES	PER CENT
71-80	82	21	27.6
81-90	16	4	25.0
Over 90 (91 and 93)	2	1	50.0

in the number of painless coronary syndromes with advancing years. They found that painless occlusion and infarction are likely to result from slowly progressive fibrotic narrowing of the coronary vessels.

It is interesting to contrast the electrocardiographic findings in this old-age group with those in another group in which the ages ranged from 20 to 35. Shipley and Halloran⁷ studied 200 normal men and women in the latter age group, using the same careful basis for selection as in the present series. Their subjects had normal blood pressure readings, normal physical findings, no history of cardiorenal disease, and good tolerance to exercise. The marked electrocardiographic changes occurring in 26 per cent of our aged subjects were not found in a single instance in this group of 200 younger people.

There is sufficient evidence that changes in the electrocardiogram take place normally in the ageing heart. These changes include a tendency for the action current to become more horizontal, for the voltage to decline, and for the T waves to be lowered, and toward an increase in the duration of the QRS and P-R intervals.⁸ These moderate changes in the electrocardiographic pattern may or may not indicate lesions in the heart. The profound alterations which were found in 26 per cent of our cases cannot be regarded simply as a part of the process of senescence. It is believed proper to assume that they represent some abnormality of the heart. If a routine electrocardiographic study were made on aged patients who have no symptoms or signs of cardiac disturbances, it would be possible to recognize the fact that approximately one-fourth of them have heart disease.

SUMMARY

An electrocardiographic study was made on 100 men and women who, in so far as could be ascertained by a careful history and physical examination, had no heart disease. Eighty-two were in the eighth decade, sixteen in the ninth, and two in the tenth. Sixty-four were men, and thirty-six were women. Twenty-six per cent showed distinct electrocardiographic abnormalities. It is evident from this study that approximately 25 per cent of apparently healthy men and women over the age of 70 probably have considerable myocardial damage.

REFERENCES

1. Willius, F. A.: The Heart in Old Age, *Am. J. Med. Sci.* 182: 1, 1931.
2. Gelman, I., and Brown, S.: Electrocardiographical Characterization of the Heart in Old Age and in Childhood, *Acta Med. Scandinav.* 91: 378, 1937.
3. Pardee, H. E. B., and Price, L.: Relation of Myocardial Disease to Abnormalities of the Ventricular Complex of the Electrocardiogram, *AM. HEART J.* 15: 28, 1938.
4. Aschoff, L.: Krankheiten des Greisenalters, zur normalen und pathologischen Anatomie des Greisenalters, *Med. Klin.* 33: 353, 1937.
5. Nathanson, M. H.: The Electrocardiogram in Coronary Disease, *AM. HEART J.* 5: 257, 1930.
6. Gorham, L. W., and Martin, S. J.: Coronary Artery Occlusion With and Without Pain, *Trans. of the Assn. of Am. Phys.* 53: 129, 1938.
7. Shipley, R. A., and Halloran, W. R.: The Four-Lead Electrocardiogram in Two Hundred Normal Men and Women, *AM. HEART J.* 11: 325, 1936.
8. Cohn, A. E.: Problems of Ageing. Cardiovascular System and Blood, edited by E. V. Cowdry, Baltimore, 133 pp. (Chapter 7), 1939, The Williams and Wilkins Co.

NICOTINIC ACID: ITS ACTION ON THE PERIPHERAL VASCULAR SYSTEM

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NICOTINIC acid and its compounds have been used successfully in the treatment of canine black tongue,¹ pellagra,²⁻⁵ and high-tone deafness.⁶ Observers have been unanimous concerning the occurrence of a sensation of heat and flushing following the use of this drug. In each case, the reaction was of short duration, occurred within a few minutes after the ingestion of as little as 30 mg., and disappeared within thirty minutes. Spies, Bean, and Stone³ found, in the majority of their cases, that this reaction coincides with an actual increase in the surface temperature of the face and neck, and a decrease in the temperature of the hands and feet.

In view of this apparent action on the peripheral blood vessels, the possibility that the drug might be used in the treatment of peripheral vascular diseases was investigated.

Fifteen adults were given 30 to 120 mg. of nicotinic acid by mouth. The effect on surface temperatures, oscillogram readings, pulse and respiratory rates, oral temperatures, and blood pressure was observed before, and from ten to thirty minutes after, the ingestion of the drug. The observations were made under standard conditions, after the subjects had rested for forty-five to sixty minutes in the recumbent position in a room kept at a constant temperature (70° F.). The body weights were all within normal limits. None of the subjects was acutely ill. There were nine women and six men in the series. Of these, four were normal; three had thromboangiitis obliterans; three, arteriosclerosis obliterans; one, essential hypertension; one, menopausal syndrome; and three, vasospastic disorders.

There were no prolonged untoward effects in any of the cases. Flushing and a sensation of heat, when they occurred, appeared in from seven to ten minutes, and disappeared within thirty minutes; they were more severe and lasting with the larger doses of the drug. Transitory tingling of the face and ears, itching, a sensation of heat over the arms and back, and slight dizziness were noted occasionally. There was no appreciable effect on blood pressure except in two cases, in which it was markedly lowered. In no instance was it raised. Respiratory and pulse rates and oral temperatures varied slightly. From the tabulation it can be seen that, regardless of the amount of the drug and the condition of the patient, surface temperatures were very inconstant. Reddening and flushing of the skin may occur with

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Received for publication June 17, 1939.

TABLE I
EXPERIMENTAL OBSERVATIONS
RESPIRATORY AND PULSE RATES, ORAL TEMPERATURE, AND BLOOD PRESSURE DID NOT CHANGE, OR CHANGED ONLY SLIGHTLY, UNCHANGED OR MINIMAL UNLESS OTHERWISE STATED

CASE	AGE AND SEX	DOSE	DIAGNOSIS	SURFACE TEMPERATURES	OSCILLOMETER READINGS	REACTIONS
1	50 F	30 mg.	Normal	Face, fingers, toes unchanged.	Slight decrease in both calves and ankles, 0.1 to 0.8 division points.	None.
2	35 F	30 mg.	Normal	Face increased 1.4 to 1.8° Cent. Fingers showed slight increases and decreases. Toes decreased 0.1 to 2.0° C.	Calves unchanged. Ankles decreased 0.4 to 0.5 div. points.	Face flushed with sensation of heat.
3	40 F	60 mg.	Vasospastic disorder of hands (Raynaud's Syndrome).	Face decreased 0.2 to 0.5° C. Fingers decreased 0.5 to 2.0° C. Toes decreased 0.1 to 1.0° Cent.	Left calf, ankle no change. Right calf and ankle decreased 0.5 to 1.4 division points.	None.
4	50 M	60 mg.	Thromboangiitis obliterans.	Face and fingers no change. Toes decreased 0.3 to 1.6° C.	No change except left ankle decreased 1.3 division points.	Flushing of face with tingling. Oral temp. reduced from 98.2°F. to 97.4°F.
5	20 F	80 mg.	Normal.	Face increased 0.5 to 0.7° C. Fingers decreased 0 to 1.2° C. Toes decreased 0 to 0.6° C.	All decreased from 0.1 to 1.5 division points (Fig. 1).	Entire right half of body to the knee, flushed, warm with itching. Left side, neck was warm.
6	60 M	80 mg.	Hypertension. Arteriosclerosis obliterans.	Not done.	Right arm decreased 3.3 div. pts. Both calves unchanged. (Fig. 1.)	Slight itching and flushing of face. Blood pressure dropped from 225/113 to 160/95.
7	16 F	80 mg.	Vasospastic disorder of feet.	Face decreased 0.9 to 1.8° C. Fingers increased 0 to 2.0° C. Toes decreased 0 to 1.5° C.	All decreased 0.2 to 1.9 div. points. (Fig. 2.)	None except for flushing of forehead with sensation of cold.
8	35 F	100 mg.	Vasospastic disorder of hands (Raynaud's syndrome).	Face increased 0.5 to 1.5° C. Fingers decreased 0.8 to 3.0° C. Toes decreased 0.2 to 1.1° Cent.	No change except for very slight decreases.	Flushing of face with itching and tingling.

TABLE I—CONT'D

CASE	AGE AND SEX	DOSE	DIAGNOSIS	SURFACE TEMPERATURES	OSCILOMETER READINGS	REACTIONS
9	63 M	100 mg.	Arteriosclerosis obliterans.	Face increased 0 to 0.7° C. Fingers decreased 0.8 to 3.0° C. Toes increased 0.1 to 1.3° Cent.	Not done.	Flushing of face with itching and tingling.
10	61 M	100 mg.	Arteriosclerosis obliterans.	Face decreased 0.4 to 1.2° C. Fingers increased 1.3 to 1.8° C. Toes unchanged.	Left ankle and right calf unchanged. Right ankle and left calf decreased 1.0 div. points.	Flushing of face with itching and tingling.
11	45 M	100 mg.	Thromboangiitis obliterans.	Face decreased 0.4 to 0.6° C. Fingers and toes very slight changes.	Right calf increased 0.2 div. pt. Left calf increased 0.5 div. pt. (Fig. 2.)	None.
12	50 F	100 mg.	Essential hypertension.	Not done.	Not done.	Blood press. dropped from 190/100 to 110/80 within 20 minutes. Pulse remaining 64, weak and thready. Near collapse.
13	45 F	100 mg.	Menopausal syndrome.	Not done.	Left arm unchanged. Left calf increased 1.0 div. pt. Right calf decreased 1.5 div. point.	None
14	32 F	120 mg.	Normal.	Face decreased 0.6 to 1.5° C. Fingers—thumbs decreased 0.2 to 3.4° C. and little fingers increased 0.3 to 1.6° C. Toes decreased 0.5 to 1.7° Cent.	All decreased 1.2 to 2.5 div. points (Fig. 3).	Nausea within 6 minutes. Face, arms, legs became flushed resembling a sunburn with marked itching. Chills. Oral temp. dropped from 98.6° F. to 98° F. Malaise present.
15	49 M	120 mg.	Thromboangiitis obliterans. (Lumbar sympathectomy 8 years previously.)	Face increased 0.5 to 0.6° C. Fingers increased 1.1 to 2.6° C. Toes increased 0.1 to 1.6° Cent.	All decreased 0.2 to 2.0 div. points (Fig. 4).	Face flushed.

either an increase or decrease in surface temperature, with or without the sensation of warmth. In Cases 7 and 14 the face became red and flushed, but the surface temperature decreased, and the sensation was one of cold. The amplitude of the oscillometric tracings diminished in the majority of the cases, particularly when large doses of the

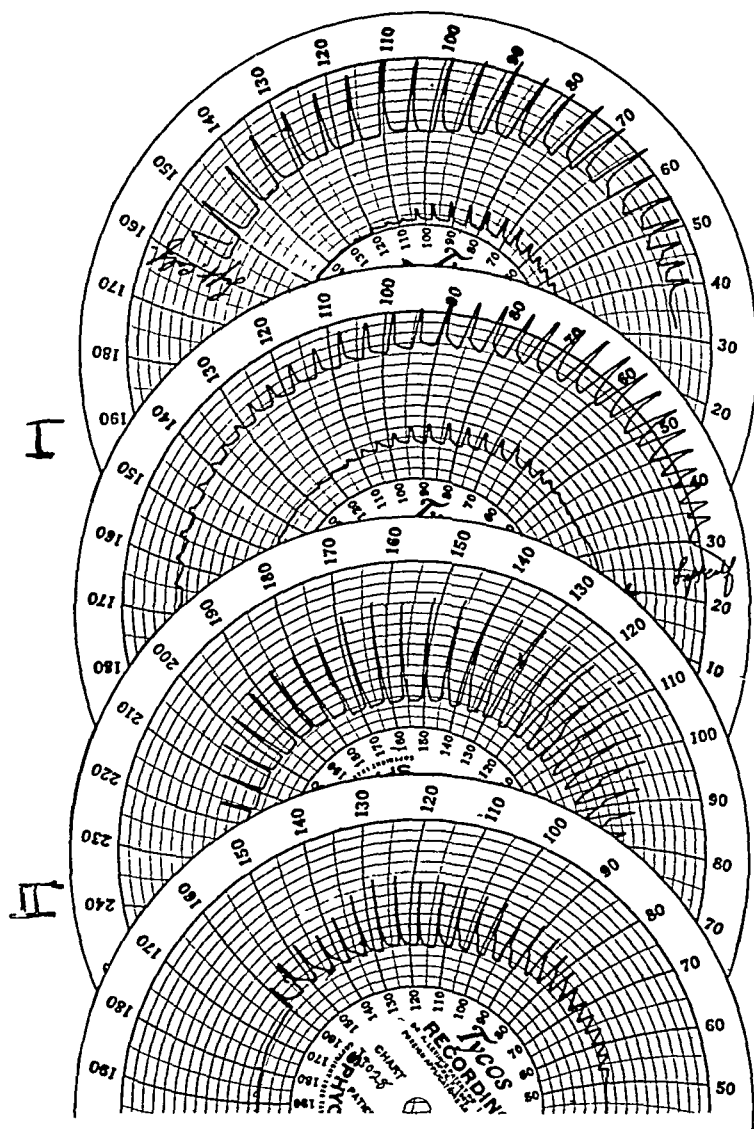


Fig. 1.—Graphs I. Upper chart: left calf and ankle at rest. Lower chart: 15 minutes after 80 Mg. nicotinic acid. Marked reduction of amplitude of tracing from first reading in calf. Subject was a normal woman, 20 years old.

Graphs II. Upper chart: right arm at rest. Lower chart: 10 minutes after 80 Mg. nicotinic acid. Blood pressure dropped from 225/113 to 160/95, as shown in the tracing. Subject was a 60-year-old man, suffering from hypertension and arteriosclerosis obliterans.

drug were used. The diminution varied from slight to marked in eleven of the thirteen cases in which tracings were recorded. These changes were not absolutely consistent. In two cases there was a definite increase in amplitude. Untoward reactions, while alarming in one subject (Case 12), were of short duration. One subject (Case 14) was rendered extremely uncomfortable by chills and a fall of body

temperature. In all of the subjects the effects of the drug had disappeared completely within thirty to forty minutes. In many instances the peak of the reaction was very short, lasting less than ten minutes.

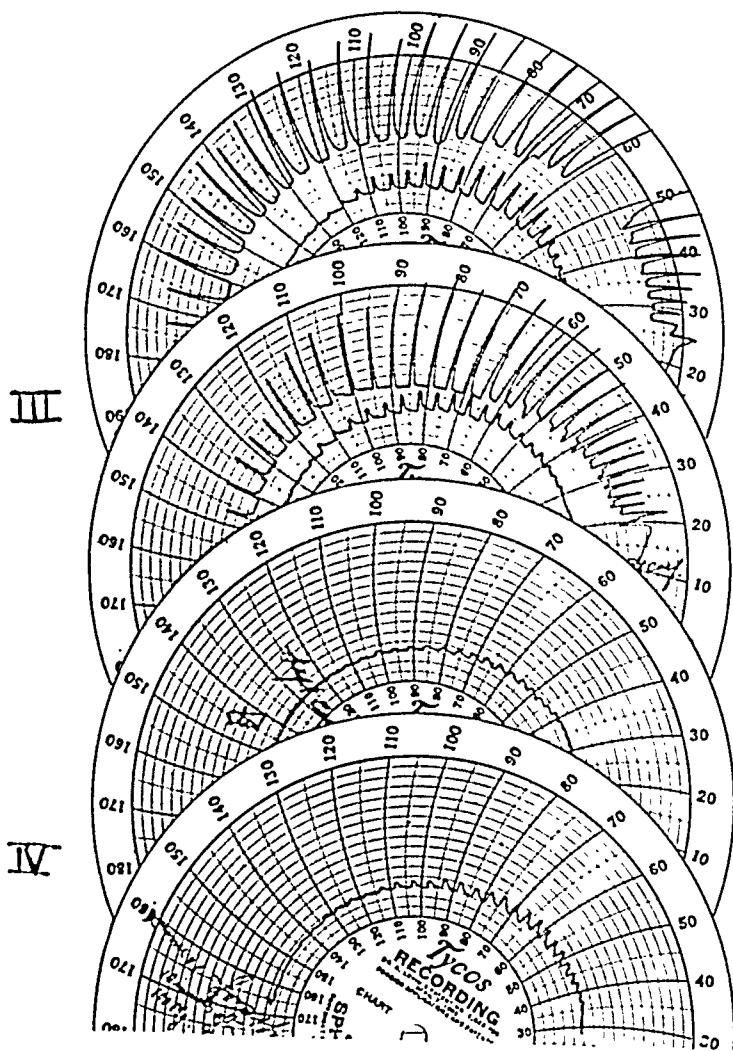


Fig. 2.—Graphs III. Upper chart: right calf and ankle at rest. Lower chart: 15 minutes after 80 Mg. nicotinic acid. Generalized reduction in amplitude. Patient was a girl, 16 years old, suffering from severe Raynaud's disease of the lower extremities.

Graphs IV. Upper chart: left calf at rest. Lower chart: 15 minutes after 100 Mg. nicotinic acid. This was one case in which increased pulsation occurred. Patient was a man, 45 years old, suffering from thromboanglitis obliterans.

COMMENT

The discordant results are difficult to explain. Other observers^{3, 4} have noted surface-temperature changes, cardiovascular and gastrointestinal symptoms, substernal oppression, and pruritus or other skin manifestations. They have attributed some of their findings to a histamine or a parasympathetic action of the nicotinic acid. The discordant results of this study may have been due to individual differences in susceptibility, to variations in the rate of absorption of the

drug from the gastrointestinal tract, and to the fact that the observations, especially the surface temperature measurements, were made at certain arbitrarily selected times.

Although it is difficult to reconcile the decreased oscillometric readings and the occasional marked fall in blood pressure with a parasympathetic effect, a histamine⁷ action does apparently account for most of the phenomena observed. Many unrelated substances

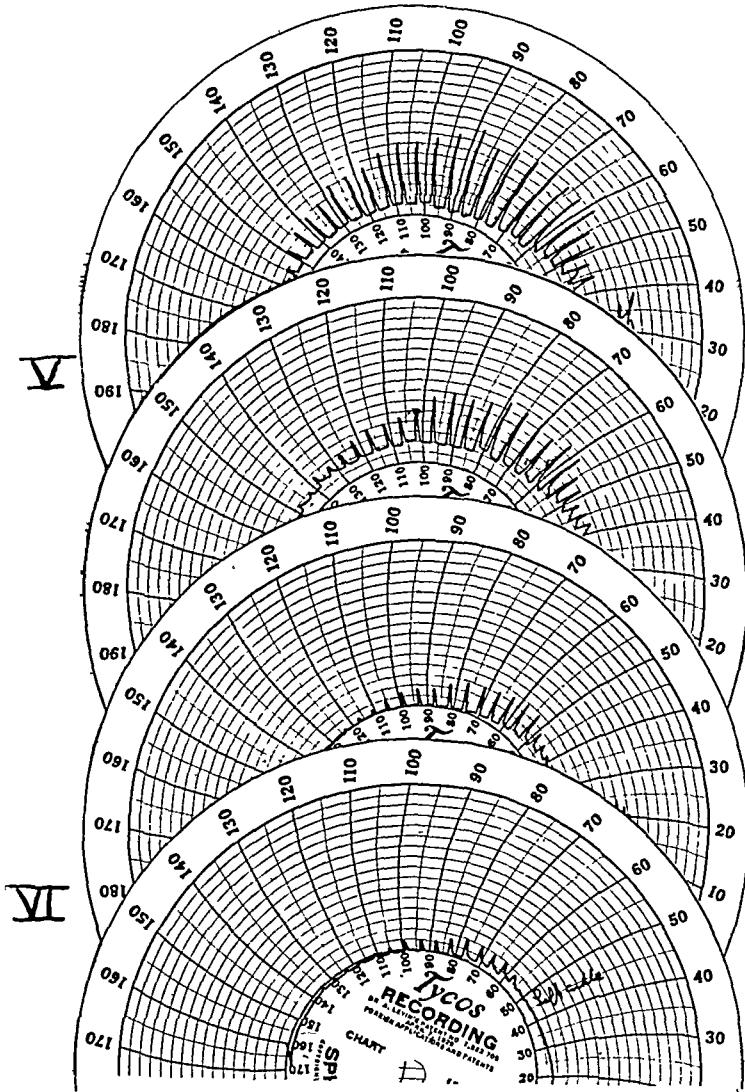


Fig. 3.—Graphs V. Upper chart: right calf at rest. Lower chart: 15 minutes after 120 Mg. nicotinic acid.

Graphs VI. Upper chart: left ankle at rest. Lower: 15 minutes after 120 Mg. nicotinic acid.

All pulsations were reduced in amplitude. These recordings were from the same subject, a normal woman, 32 years of age.

give this reaction. They include tissue extracts, secretin, peptones and other products of protein cleavage, blood serum, and bacterial products. It also occurs in traumatic shock. Histamine causes a contraction of smooth muscle regardless of its innervation, and an increased permeability and dilatation of the capillary bed. This action

is clearly apparent in the majority of the cases observed, and occurs even after sympathectomy (Case 15). Substernal oppression may be the result of coronary artery constriction, although electrocardiographic tracings have been reported to show nothing abnormal.³ The lowered surface temperature observed when the skin is flushed and red may be due to stasis of blood in the engorged capillary bed. A further pharmacologic action of histamine is an initial stimulation

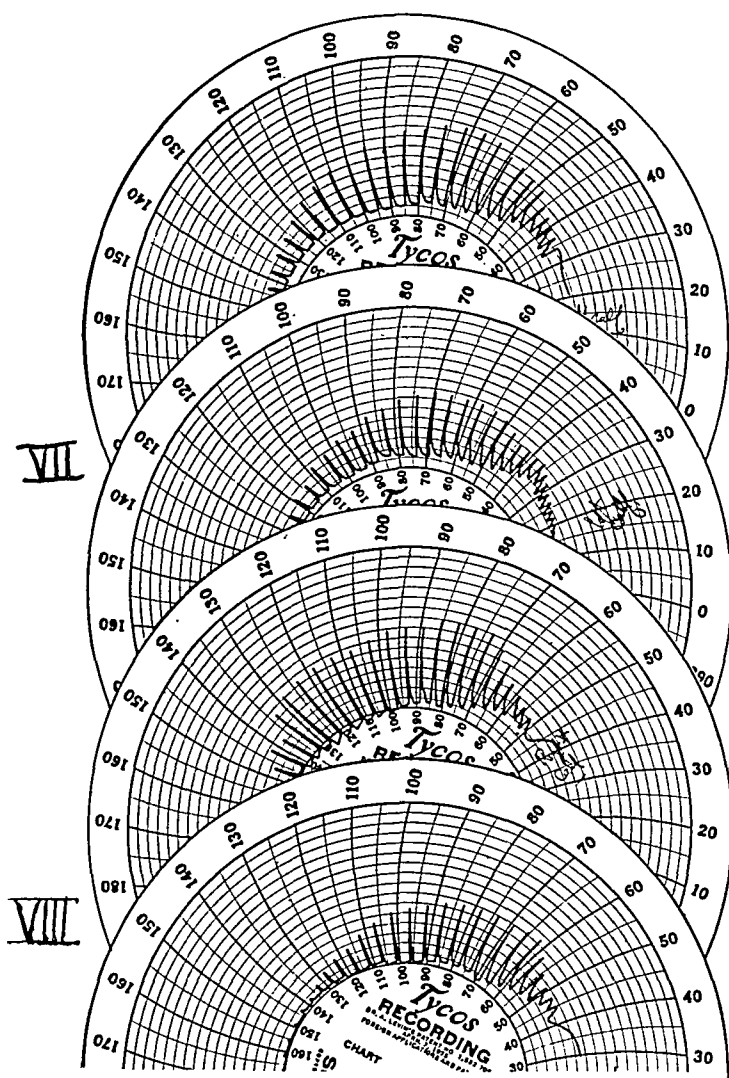


Fig. 4.—Graphs VII. Upper chart: left calf at rest. Lower: 15 minutes after 120 Mg. nicotinic acid.

Graphs VIII. Tracings from right calf, before and after nicotinic acid, in the same individual. All pulsations are reduced in amplitude. Patient was a man, 49 years old, suffering from thromboangiitis obliterans. He had had a lumbar sympathectomy eight years previously.

of the gastrointestinal tract, followed by a relaxation. This may explain the nausea, vomiting, belching, and other gastrointestinal symptoms reported by most observers. Spies, et al.,³ injected nicotinic acid intracutaneously in normal subjects, thereby obtaining wheals and pruritus which were similar to those produced by histamine.

SUMMARY

1. Nicotinic acid, administered orally, in single doses, in the majority of cases causes transitory flushing of the skin, tingling, itching, and sensations of heat, regardless of the condition of the subject or the size of the dose.

2. The changes in the surface temperature of the face, fingers, and toes are variable and unpredictable.

3. The amplitude of the oscillometric tracings is diminished in the majority of cases, and the degree of diminution varies directly with the quantity administered.

4. It is suggested that the effects of nicotinic acid are similar to those produced by histamine.

5. Nicotinic acid is of little value in the treatment of peripheral vascular disease because it produces uncomfortable symptoms and arterial constriction, and because whatever favorable effects it may have are of very short duration.

REFERENCES

1. Elvehjem, C. A., Madden, R. J., Woolley, D. W., and Strong, F. M.: Relation of Nicotinic Acid and Nicotinic Acid Amide to Canine Black Tongue, *J. Am. Chem. Soc.* 59: 1767, 1937.
2. Smith, D. T., Ruffin, J. M., and Smith, Susan G.: Pellagra Successfully Treated With Nicotinic Acid, *J. A. M. A.* 109: 2054, 1937.
3. Spies, T. D., Bean, W. B., and Stone, R. E.: Treatment of Subclinical Classic Pellagra. The Use of Nicotinic Acid, Nicotinic Acid Amide and Sodium Nicotinate With Special Reference to the Vasodilator Action and the Effect on Mental Symptoms, *J. A. M. A.* 111: 584, 1938.
4. Sebrell, W. H., and Butler, R. E.: A Reaction to the Oral Administration of Nicotinic Acid, *J. A. M. A.* 111: 2286, 1938.
5. Rachmilewitz, M., and Glueck, Helen: Treatment of Pellagra With Nicotinic Acid, *Brit. M. J.* 2: 346, 1938.
6. Selfridge, G.: Nicotinic Acid and the Eighth Nerve: Preliminary Report, *Ann. Otol. Rhin. and Laryng.* 48: 39, 1939.
7. Sollmann, T.: *Manual of Pharmacology*, Philadelphia, 1937, W. B. Saunders.

THE INCIDENCE OF ORGANIC HEART DISEASE IN SCHOOL CHILDREN*

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MANY surveys to determine the incidence of heart disease in school children have been conducted in various parts of the United States. We have examined the children of the Cincinnati schools in order to compare the incidence of organic heart disease in this city with that of other communities. In localities where rheumatic fever is prevalent, about 80 per cent of the children with organic heart disease have rheumatic valvulitis, and the remainder, congenital lesions. This ratio has been accepted so frequently that we believed it wise to investigate the point further in a community such as ours, where rheumatic fever is less severe than in many eastern and northern cities.

Since a previous survey of the same type, but on a smaller scale, had been conducted in this city in 1927, by Benjamin,¹ we were anxious to observe any changes of incidence rates which might have occurred during the interval of 10 years.

PROCEDURE

During a 2-year period, beginning in the fall of 1936, the school physicians referred for special examinations all children whom they suspected of having any cardiac abnormality. This group of patients was re-examined by one of four pediatricians, all of whom were especially interested in cardiology and were attending physicians to the Children's or General Hospital cardiac clinic. The children were stripped to the waist and examined in the reclining and sitting positions, and in the standing position before and after exercise. The examination included percussion and auscultation of the heart, determination of the heart rate and blood pressure, estimation of the nutritional status, inspection of the mouth and throat, palpation for tonsillar lymph nodes, and observation for cyanosis and clubbing of fingers. Electrocardiograms, teleoroentgenograms, and fluoroscopic examinations were obtained in doubtful cases whenever possible. Historical data, obtained from the parents by visits of the school nurse to their homes, included the age at which heart disease was first noted, the occurrence of cyanosis or cyanotic attacks, symptoms of the rheumatic state, and whether the child had had a tonsillectomy, diphtheria, or scarlet fever.

RESULTS

Incidence.—A total of 85,389 children in 157 schools were examined by the school physicians during the 2-year period, and 1,782 of these children had some clinical finding suggestive of heart disease. When

*This survey was sponsored by the Cincinnati Heart Council and the Cincinnati Board of Health, and was made possible by special contributions from the Union Central and the Western and Southern Life Insurance Companies.

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Received for publication June 19, 1939.

this group was re-examined by us, 633 were found to have normal hearts, 700 to have murmurs which were believed to be only functional or accidental in type, and 449 to have definite evidence of cardiac disease. This last group constituted 25.4 per cent of the patients selected by the school physicians, or 0.53 per cent of the entire number of children (Table I).

TABLE I
THE INCIDENCE OF CARDIAC LESIONS IN SCHOOL CHILDREN

I. Total number examined by school physicians		85,389		
Public elementary schools		43,146		
Catholic elementary schools		17,565		
Public junior and senior high schools		19,047		
Catholic high schools		2,008		
Special and trade schools		3,623		
II. Number with suspected heart disease			1,782	2.09%
III. Reclassification, at special examination, of these 1,782 patients.				
Normal hearts		633—35.5%		
Functional or accidental murmur		700—39.2%		
Abnormal hearts		449—25.2%		
IV. Number with definite evidence of heart disease			449	0.53%
A. Organic		304		0.36%
Acquired	170	301 {		0.20%
Congenital	131			
Unclassified	3			
				0.15%
B. Possibly organic (Class E)		109	less than	0.01%
Possibly acquired		81		0.12%
Possibly congenital		28		0.09%
				0.03%
C. Extrasystoles		41		0.04%
(5 included in above categories also)				

Children with tachycardia and hypertension were not included in the group with cardiac lesions because of the great lability of the pulse rates and blood pressures of children under conditions of excitement and fear. From single examinations, the diagnosis of these abnormalities did not seem justifiable.

Of the 449 children with heart disease, 304 had definite evidence of organic lesions (0.36 per cent of the total number of 85,389 children); 109 were classified as possibly having organic disease but requiring further observation to complete the diagnosis; and 41 had extrasystoles (Table I). The diagnosis of "potential heart disease" was purposely omitted because of the lack of complete histories in each case.

Race, Sex, and Age Distribution.—The incidence of *acquired heart disease* was found to be almost twice as high among the colored children as among the white children (Table II). This difference was shown to be statistically significant (employing a fourfold table and the Chi square formula). This is contrary to the observations of other investigators. Wood, Jones, and Kimbrough² found rheumatic heart disease less common among the negro population of Virginia than among the white population. Wilson, Lingg, and Croxford³ analyzed the records of 500 chil-

dren attending the heart clinic at Nursery and Child's Hospital in New York City. Although this clinic drew its patients from a negro district, only 4.6 per cent of the children enrolled as cardiac patients were negroes. Sutton⁴ found that the percentage of negro children in the general pediatric clinic of Bellevue Hospital, New York City, was three times that in the clinic for patients with heart disease. Ash,⁵ in a study of the records of all rheumatic patients treated in the wards or heart clinic, over a ten-year period, at the Children's Hospital in Philadelphia, found that 83 per cent of the rheumatic patients were white, and 17 per cent were negroes, while among the total number of all patients in the dispensary and wards of the hospital the distribution between the two races was equal.

Acquired heart disease was more common in girls than in boys (Table II).

TABLE II
RACE, SEX, AND AGE DISTRIBUTION

	TOTAL NUMBER SCHOOL CHILDREN	ACQUIRED LESIONS NUMBER PER CENT	CONGENITAL LESIONS NUMBER PER CENT
<i>Race</i>			
White	73,074	191 0.26	140 0.19
Black	12,315	60 0.49	19 0.15
Total	85,389	251 0.29	159 0.19
<i>Sex</i>			
Male		114 (45.4 per cent of 251)	80 (50 per cent of 159)
Female		137 (54.6 per cent of 251)	79 (50 per cent of 159)
Total		251	159
<i>Age</i>			
5-9 yr.	23,995	13 0.054	38 0.158
10-14 yr.	26,536	75 0.282	46 0.172
15-18 yr.	14,369	48 0.333	22 0.153
Total	64,900	136	106

Data in regard to age distribution could be obtained only from the public schools. The low incidence of acquired heart disease in the group under 10 years of age and the highest incidence in children of high school age were to be expected.

Congenital heart disease was fairly equally divided among the race, sex, and age groups (Table II).

Histories.—An analysis of the histories of the children with acquired heart disease indicated that 66 per cent of children with definite cardiac lesions had had one or more rheumatic symptoms, while only 3.6 per cent of the children with doubtful lesions had had similar symptoms (Table III). Negative histories were much more frequent (36.1 per cent) in the doubtful cases than in those in which there were definite cardiac lesions (8.9 per cent).

TABLE III
HISTORIES OF CHILDREN WITH ACQUIRED HEART DISEASE

	ACQUIRED HEART DISEASE		POSSIBLY ACQUIRED HEART DISEASE	
	NO. PTS.	PER CENT	NO. PTS.	PER CENT
Rheumatic fever (chiefly polyarthritis)	89	52.3	1	1.2
Chorea	9	5.2	2	2.4
			66.0	
Rheumatic fever and chorea	10	5.8	-	-
Chorea and growing pains	4	2.3	-	-
Growing pains only	17	10.0	14	17.2
Tonsillitis only	9	5.2	12	14.8
Scarlet fever	6	3.3	7	8.6
Heart disease noted following infections, such as grippe and pneumonia			2	2.4
History negative	15	8.9	29	36.1
No history available	11	6.4	14	17.2
Total	170		81	

Interesting to note in the histories of the children with congenital heart lesions is the fact that in about 55 per cent the condition was noted at birth or during the first two years of life, and that in 24 per cent the condition was not detected until school age (Table IV).

TABLE IV
HISTORIES OF CHILDREN WITH CONGENITAL HEART LESIONS

TIME HEART DISEASE WAS NOTED	NUMBER OF CHILDREN	PER CENT
At birth	28	29.4
Between first month and second year	24	25.2
During third year	5	5.3
During fourth year	5	5.3
During fifth year	10	10.5
After fifth year	23	24.2
Total	95	
No history available	36	
Total	131	

Economic Levels.—It was possible to group the children with acquired heart disease into four economic levels, according to small census tracts which have been outlined in this city. Group one had the lowest economic status, and group four the highest. A total of 146 cardiac children, 10 to 19 years of age, was compared with the total population of the same age in the respective economic locations, employing the figures of the 1935 census. The mean incidence rate of acquired heart disease for the entire group was 0.20 per cent, and the probable error was $\pm .029$. When we consider the individual groups, it is obvious that the incidence rates at the two lowest economic levels were significantly high, that the rate for the group with the highest economic status was significantly low, and that that of the third group falls so close to the standard deviation that it is probably not significant (Table VIII).

Anatomic Diagnoses.—Of the 170 children with acquired heart disease, 68 per cent had mitral insufficiency alone. A diagnosis of mitral insuf-

fiency was made on the basis of a systolic murmur at the apex transmitted toward or into the axilla, and persisting or increasing in intensity on change of position from the reclining to the erect position and after exercise. In none of these patients was a diastolic murmur present. A list of all of the diagnoses is given in Table V.

Of the 131 children with congenital heart disease, even with the aid of fluoroscopy and electrocardiography, an anatomic diagnosis was impossible in thirty-two. Patent ductus arteriosus was diagnosed in 25.1 per cent of the cases, and interventricular septal defects in 38.1 per cent. The latter group represents those cases in which a fairly rough, long, loud, high-pitched systolic murmur was heard over the precordium, loudest in the third or fourth intercostal space just to the left of, or over, the sternum, with or without the accompaniment of a thrill. It is quite possible that in some instances this anatomic diagnosis was incorrect. Of the children with congenital lesions, cyanosis was slight in eight instances, moderate in five, and marked in six.

Medical Care.—The type of medical care of 413 children (excluding those with premature contractions) is shown in Table VII. There were 39.0 per cent who were under the care of private physicians, 9.2 per cent who had received no medical attention at the time of the survey, and the remainder were being observed and treated in heart clinics or special schools and institutions.

TABLE V
ANATOMIC DIAGNOSES IN CHILDREN WITH ACQUIRED HEART DISEASE

	NUMBER	
Mitral insufficiency	116	68%
Mitral stenosis	2	
Mitral insufficiency and stenosis	15	
Mitral insufficiency and probably stenosis	7	
Mitral insufficiency and aortic insufficiency	9	
Mitral insufficiency and aortic stenosis	1	
Mitral insufficiency and stenosis and aortic insufficiency	5	
Aortic insufficiency	8	
Aortic insufficiency and stenosis and possibly mitral insufficiency and stenosis	3	
Mitral insufficiency and stenosis and aortic stenosis	1	
Intraventricular block	1	
Mitral insufficiency and stenosis and tricuspid insufficiency	1	
Rheumatic heart disease— <i>anatomic diagnosis not known</i> (refused examination)	1	
Total	170	

Control Study.—At the completion of the survey it was felt that some further study of the validity of our statistics should be attempted. For this purpose an elementary school representing a fair cross section of economic levels was chosen, and the four special clinicians examined every child in the school, from the kindergarten class through the eighth grade.

Of a total of 709 children examined, four were found to have definite signs of organic heart disease, and five others had to be classified as hav-

TABLE VI
ANATOMIC DIAGNOSES IN CHILDREN WITH CONGENITAL HEART DISEASE

	NUMBER	PER CENT
Dextrocardia	2	1.5
Dextrocardia and pulmonary stenosis	1	0.8
Interventricular septal defect	50	38.1
Interventricular septal defect and possibly heart block	1	0.8
Patent ductus arteriosus	33	25.1
Patent ductus and rheumatic heart disease—mitral insufficiency	1	0.8
Septal defect and patent ductus	2	1.5
Aortic stenosis	1	0.8
Pulmonary stenosis	7	5.3
Pulmonary stenosis or patent ductus	1	0.8
No diagnosis	32	24.4
Total	131	

TABLE VII
MEDICAL CARE OF 413 CHILDREN

	PRIVATE PHYSICIAN	NO PHYSICIAN	CONDON* SCHOOL	FREE CLINICS
Acquired	42	12	28	88
Congenital	65	8	19	39
Possibly acquired	40	12		29
Possibly congenital	15	6		7
Unclassified			2	1
Total	162	38	49	164
Per cent	39.0	9.2	51.8	

*Special school for handicapped children.

TABLE VIII
MORBIDITY RATES IN ACQUIRED HEART DISEASE IN THE SCHOOL SURVEY, CLASSIFIED
ACCORDING TO ECONOMIC STATUS OF THE POPULATION

ECONOMIC STATUS	CHILD POPULATION 10 TO 19 YEARS OF AGE	PATIENTS 10 TO 19 YEARS OF AGE	PER CENT
Group 1 (lowest level)	19,481	62	0.32
Group 2	13,501	48	0.26
Group 3	17,987	26	0.14
Group 4 (highest level)	15,843	10	0.063

ing “possible organic heart disease” (Class E). When the figures of incidence in this group were compared with those of the entire survey, the statistical analysis indicated that the incidence of organic heart disease in the control sample was not significantly greater than that in the entire survey, but a significantly greater number of children with “possible heart disease” were uncovered in the control sample than in the general survey. It is possible, therefore, that the incidence of borderline cases, classified as “possible heart disease,” in our general survey is too low. The school physicians in their routine examinations of children may have overlooked some of the minor cardiac defects. This may perhaps be explained by the following facts: (a) the school examinations have, until recently, been made with the children’s clothes loosened, but

TABLE IX

 INCIDENCE OF HEART DISEASE IN SCHOOL CHILDREN OF OTHER CITIES
 (REPORTS ARRANGED IN CHRONOLOGICAL ORDER)

	TOTAL SCHOOL POPULATION EXAMINED	ORGANIC HEART DISEASE PER CENT	RHEUMATIC HEART DISEASE PER CENT
New York City, 1915 ⁶	278,174	1.50	
New York City, 1918 ⁷	250,000	1.60	1.28 *
New York City, 1918 to 22 ⁷	1,336,343	1.39	1.112*
New York City, 1921 ⁸	44,000	0.50	0.40 *
Chicago, 1923 ⁷	158,826	0.90	0.720*
Philadelphia, 1924 ⁹	23,671	0.63	0.504*
Chicago, 1924 ⁷	153,671	1.50	1.20 *
Chicago, 1925 ⁷	130,260	1.70	1.36 *
Boston, 1927 ¹⁰	119,337	0.52	0.45
Philadelphia, 1929 ¹¹	10,333 (B)	0.91	0.76
Florida, Illinois and Missouri, 1929 ¹²	17,974	1.00	0.80 *
Cincinnati, 1927 ¹	6,960	0.37	0.296*
Rochester, Minn., 1931 ¹³	1,328 (A)	0.70	0.560
New York City, 1931 ¹⁴	2,691 (C)	1.10	0.88 *
New Haven, 1934 ¹⁵			
<i>Grade</i> <i>Children</i>		(Systolic Murmur)	
"Better School" 1	1,144	1.32	1.05 *
5	1,123	1.42	1.13 *
"Poorer School" 1	1,863	1.93	1.54 *
5	1,628	2.08	1.68 *
Philadelphia, 1937 ¹⁶ (Elementary)	33,293	0.50	
		(E) 0.30	
		(F) 0.12	
(High School)	9,154	0.90	
		(E) 0.40	
		(F) 0.20	
New Mexican Indians, 1937 ¹⁷	1,019	--	0.50
Northern Indians, 1937 ¹⁷	688	--	4.50
San Francisco, 1938 ¹⁸	13,338	0.37	0.22
Cincinnati, 1938	85,389	0.36	0.20
		(E) 0.12	

*Rheumatic heart disease computed as 80 per cent of all organic cases.

(A) Ages 11 to 20

(B) Ages 6 to 18

(C) Ages 14 17

(E) "Possible heart disease"

(F) "Potential heart disease."

not removed, (b) the examinations have been made with the children in the standing position only, and (c) it is possible that insufficient attention has been paid to the heart in routine school examinations. It must be remembered, also, that the four clinicians participating in this survey were pediatricians with special training in cardiology, who were looking for abnormal cardiac signs, and were able to examine each child with extreme care.

COMMENT

In many of the school surveys of this type, no attempt has been made to divide the cases of organic heart disease into acquired and congenital groups; it was simply assumed that 80 per cent of all organic heart disease was rheumatic in origin, regardless of geographic location. These

figures were derived from the examination of children in the second decade of life who were living in the eastern part of the United States,¹⁹ and have been applied unjustifiably to conditions in other localities. This proportion of 80 per cent rheumatic heart disease does not hold true among the school children of Cincinnati, where only 55 per cent of the cases of organic heart disease could be classified as acquired, or rheumatic, in origin. The statistics from San Francisco,¹⁸ where 65.0 per cent of the organic heart disease of school children was found to be rheumatic in type, corresponded most closely to ours.

The variation in the statistics from other localities is evident (Table IX). The results depend upon the examiners, the age of the children examined, the economic status of the children, and the climate or locality in which the children live. For example, the Boston survey¹⁰ was carried out in much the same way as ours, with cardiologists as the special examiners. The comparatively low incidence of organic heart disease found (0.52 per cent) is of interest. In the New Haven survey,¹⁵ the higher incidence of acquired heart disease in the "poorer school" is well illustrated. In the Philadelphia survey¹⁶ of 1937, the higher incidence of acquired heart disease among the high school students was considerable. The difference in incidence of acquired heart disease which depends on climate is illustrated in the survey carried on among the New Mexican and Northern Indians.¹⁷ The incidence among the Northern Indians was nine times higher than that among the New Mexican Indians. Our figures agree closely with those of the survey previously carried out in this city,¹ except in respect to etiology. In the previous study, acquired heart disease had been assumed to constitute 80 per cent of all organic heart disease in children in the second decade of life.

SUMMARY

1. Of a total of 85,389 children, 5 to 19 years of age, who were examined by school physicians, 1,782 were suspected of having heart disease.

2. Re-examination of this group of 1,782 by a group of pediatricians indicated that 449 (0.53 per cent of the total school population) had organic lesions, and 700 others had functional or accidental murmurs. The remaining 633 children had normal hearts.

3. Of the 301 children with organic lesions, acquired heart disease, probably rheumatic in origin, occurred in 55 per cent, and congenital lesions in 45 per cent.

4. Acquired heart disease was more prevalent in the negro than in the white race. It occurred more frequently in girls than in boys, and more often in children living under poorer economic conditions than in those whose economic status was better. The incidence of congenital heart disease was independent of race or sex, and was fairly equally distributed among the different age groups studied.

5. About 24 per cent of the parents of children with congenital heart disease had been totally unaware of the existence of these lesions until the school examinations were made.

6. The results of cardiac examinations by the school physicians were compared with those made by a special group of pediatricians in a sample of the school population. Both groups discovered approximately the same number of children with definite lesions, but the physicians especially interested in cardiology detected more borderline cases of "possible heart disease."

7. A comparison of the results of this study with previous school surveys indicates that there are wide variations of incidence in different localities. The statement that 80 per cent of the acquired lesions are rheumatic in origin is true only in areas where rheumatic fever is prevalent and severe, and cannot be universally employed as a distribution figure.

I wish to express my gratitude to my colleagues who aided in the examinations, Doctors Margaret Posey, Carl Koch, and Irvin Itkoff. In addition, I wish to thank Mrs. Catherine Kavel, nurse to the cardiac clinics, who visited the schools with us, for her untiring efforts; Miss Minnie Landon, for aid in the compilation of statistics; Mrs. William Brown, for her assistance in the statistical analysis; Dr. Floyd Allen, for preparing the data on the economic distribution of the patients; Dr. Julien Benjamin, for his help and advice; Doctor Harder, Acting Health Commissioner, and the School Physicians, for their cooperation; and Mrs. Tooker and the Board of Health nurses, for their help in the school examinations and for obtaining histories in the cardiac cases.

REFERENCES

1. Benjamin, J. E.: Heart Disease Situation in Cincinnati, *AM. HEART J.* 2: 637, 1927.
2. Wood, J. E., Jones, T. D., and Kimbrough, R. D.: Etiology of Heart Disease; Clinical Study of 623 Cases With Observations on Race and Climate, *Am. J. M. Sc.* 172: 185, 1926.
3. Wilson, M. G., Lingg, C., and Croxford, G.: Statistical Studies Bearing on Problems in Classification of Heart Disease; Heart Disease in Children, *AM. HEART J.* 4: 164, 1928.
4. Sutton, L. P.: Observations on Certain Etiologic Factors in Rheumatism, *AM. HEART J.* 4: 145, 1928.
5. Ash, R.: Prognosis of Rheumatic Infection in Childhood; Statistical Study, *Am. J. Dis. Child.* 52: 280, 1936.
6. Holt, L. E.: The Problem of the Cardiac Child in New York City, *Arch. Ped.* 34: 12, 1917.
7. Bainton, J. H.: Heart Disease and School Life, *Am. J. Public Health* 18: 1252, 1928.
8. Halsey, R. H.: Heart Disease in Children of School Age, *J. A. M. A.* 77: 672, 1921.
9. Cohn, A. E.: Heart Disease From the Point of View of Public Health, *AM. HEART J.* 2: 275, 1927.
10. Cardiac Survey of Children in the Boston Public Schools, *The Nation's Health* 9: 21, 1927.
11. Cahan, J. M.: Incidence of Heart Disease in School Children, *J. A. M. A.* 92: 1576, 1929.
12. Clark, T.: Heart Disease a Public Health Problem, *Public Health Report* 44: 2463, 1929.
13. Hewitt, E. S., and Geddie, K. B.: Report of Physical Examination of High School Students, *Proc. Staff Meet. Mayo Clinic* 6: 53, 1931.

14. Meyers, J.: Physical Findings in New York City Continuation School Boys; Element in Vital Statistics of Adolescents, *Am. J. Public Health* 21: 615, 1931.
15. Paul, J. R., Harrison, E. R., Salinger, R., and DeForest, G. K.: Social Incidence of Rheumatic Heart Disease; Statistical Study in New Haven School Children, *Am. J. M. Sci.* 188: 301, 1934.
16. Cahan, J. M.: Rheumatic Heart Disease in Philadelphia School Children, *Ann. Int. Med.* 10: 1752, 1937.
17. Paul, J. R., and Dixon, G. L.: Climate and Rheumatic Heart Disease; Survey Among American Indian School Children in Northern and Southern Localities, *J. A. M. A.* 108: 2096, 1937.
18. Sampson, J. J., Christie, A., and Geiger, J. C.: Incidence and Type of Heart Disease in San Francisco School Children, *AM. HEART J.* 15: 661, 1938.
19. Wyckoff, J., and Lingg, C.: Statistical Studies Bearing on Problems of Classification of Heart Disease; Etiology in Organic Heart Disease, *AM. HEART J.* 1: 446, 1925-26.

A COMPARATIVE STUDY OF PRECORDIAL LEADS IV R AND IV F

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THE rapidly spreading use in recent years of supplementary precordial leads in clinical electrocardiography was unfortunately attended by much confusion arising from lack of uniformity in technique and nomenclature. In an effort to standardize practice, committees of the American Heart Association and the Cardiac Society of Great Britain and Ireland, early in 1938, jointly recommended the general adoption of a uniform apical placement of the precordial electrode, and further suggested that for all ordinary purposes the precordial (exploring) electrode be paired either with one on the right arm (lead to be known as IV R) or the left leg (lead to be known as IV F). The galvanometer connections of the latter lead were to be so made that relative positivity of the apical electrode would be represented in the finished curve by an upward deflection.¹

At the time these recommendations were made, the relative merits of Leads IV R and IV F were not yet considered established, and the committee implied that further investigation was required before one or the other could be recommended for routine clinical use.

It had been the practice for several years in this laboratory to employ a lead practically identical with Lead IV R. However, casual experiments with other leads, including IV F, indicated that occasionally significant discrepancies were encountered even between these two leads. Although convenience favored Lead IV R, since it involved only the arm leads and required no interchanging of the electrodes, it was evident that the relative clinical value of each of these leads required further clarification, and this need was considered the more urgent when the universal adoption of *either* Lead IV R *or* Lead IV F was recommended. This study was thus undertaken with the express purpose of determining which, if either, of these two leads was the more helpful clinically.

METHODS

Leads IV R and IV F were obtained together with the three conventional leads in 400 electrocardiographic examinations of 349 subjects. Selection was exercised only in the sense that the precordial leads were taken in cases of known or suspected heart disease. In all instances the electrocardiographic examination was merely incidental to a complete clinical study, and the great majority of the patients were hospitalized.

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Received for publication June 21, 1939.

Two standard laboratory models of string galvanometer electrocardiographs* were employed. For the conventional leads and the indifferent (distant) contact of the precordial leads German-silver-plated electrodes, 4 by 6 cm. in size, were strapped to the extremities. For the exploring (near) electrode of the precordial leads a grooved, silver-plated disc, 3 cm. in diameter, was held at the desired location either by an attendant or by the patient's left hand. A proprietary electrode jelly provided a contact medium by means of which skin resistance was kept below 1000 ohms in all but very few instances. Lead IV R was obtained by pairing the right arm lead with the precordial electrode applied, as recommended,¹ to the extreme outer border of the palpable apex beat, or in the fifth intercostal space just beyond the left border of cardiac dullness, or just outside the mid-clavicular line if percussion of the heart was unsatisfactory. For Lead IV F the left leg was paired with the precordial electrode again placed as above. The galvanometer string tension was adjusted in all instances so that a deflection of one centimeter in the finished record corresponded to a potential difference of one millivolt. In order to obtain "upright" electrocardiograms, the connections for Lead IV F were so made that relative positivity of the apical electrode was represented by an upward deflection in the finished curve. All records were taken with the patient reclining at an angle of about 45°. When, early in the study, dissimilar precordial electrocardiograms were obtained, the examination was often repeated to rule out error in connecting the patient; in all the instances here reported the repeated records were practically identical with the original set.

RESULTS

Among the 400 pairs of precordial electrocardiograms obtained there were sixty-four instances of significant discrepancy. For convenience in presenting the data, all of the essentially similar records were considered together, and the general characteristics of Leads IV R and IV F, as encountered in this group, are briefly presented below in Section I. The instances of dissimilar precordial electrocardiograms are separately analyzed later in Sections II and III.

SECTION I. ANALYSIS OF ESSENTIALLY SIMILAR LEADS IV R AND IV F

P Waves.—In Lead IV R the P wave was almost invariably present as an upright deflection 1 to 1.5 mm. in amplitude, and sufficiently well defined to permit ready measurement of the P-R interval. In a few records P was isoelectric, and in a few others it attained an amplitude of 2 and 2.5 mm., but in no case was it a negative deflection in this lead. In Lead IV F, on the other hand, the P wave was usually either absent (isoelectric), or was a very small, diphasic wave, too ill-defined to permit accurate measurement of the P-R interval. In approximately 5 per cent of the records, P appeared as a positive deflection 0.5 to 1.5 mm. in amplitude, and in about 12 per cent the P deflection was negative in direction and 0.5 to 1.5 mm. in depth. In no instance was the P wave in Lead IV F a larger positive or more clearly defined deflection than in Lead IV R. Lead IV R, therefore, appeared preferable to IV F for depiction of the auricular wave and A-V conduction.

*"Hindle" Electrocardiograph, Cambridge Instrument Co.

QRS Complexes.—The QRS complexes, though usually diphasic, showed a wide range of variation in direction, from totally positive to totally negative. This was not unexpected in a collection of normal and abnormal electrocardiograms taken almost indiscriminately among patients known to have or suspected of having heart disease. Of greater interest, from the standpoint of comparison of the two leads, was the observation that in practically 75 per cent of the tracings the QRS directions were essentially the same in both leads. In the remaining 25 per cent, QRS was a more positive complex in Lead IV F than in IV R in all but one instance; in this, the QRS was entirely positive in IV R and balanced in IV F. The amplitude of QRS was essentially the same in both Leads IV R and IV F in half of the records. In 35 per cent of the tracings, QRS was 2 to 20 mm. larger in Lead IV R, with an average preponderance of 6.5 mm. In the remaining 14 per cent of the records, QRS was 2 to 20 mm. larger in Lead IV F, with an average preponderance of 5 mm. for this small group. Considering all of the records, QRS averaged 1.5 mm. greater in Lead IV R than in Lead IV F. In summary, the QRS complexes of Leads IV R and IV F were similar in the majority of instances. Dissimilarity was manifested largely in a tendency for QRS in IV F to be more often a positively directed complex, but slightly smaller in amplitude than in IV R.

RS-T Features.—In approximately half of the records, the RS-T junction was one-half to several millimeters above the isoelectric line. Whether elevated, isoelectric, or low, the junction was essentially the same in both Leads IV R and IV F in 73 per cent of the records. In all of the remainder the junction was more positive in position in IV R by 0.5 to 2 mm., including four instances in which the junction occurred below the isoelectric line. In the majority of records (57 per cent) the T wave appeared to take off directly from the QRS complex. When a horizontal RS-T segment was present in one of the precordial leads it was invariably present in the other. In only slightly less than 10 per cent of all the tracings was the RS-T segment slightly longer in one lead than in the other, but when such a difference occurred it was seen approximately twice as often in Lead IV F as in IV R. In summary, the RS-T junction level was similar for Leads IV R and IV F in the great majority of instances, but in an appreciable number of records the junction was higher (more strongly positive) in Lead IV R than in IV F. Slightly less than half of the records showed a horizontal RS-T segment, but this was usually of about the same degree in both precordial leads.

T Waves.—In electrocardiograms in which the T wave was positive both in Leads IV R and IV F, it showed a definite tendency to be larger in Lead IV R. Thus, in 200 such pairs in which the T-wave amplitudes were carefully measured, 62 per cent of the records showed that T in Lead IV R exceeded that of Lead IV F by an average of 2.5 to 3 mm.,

and in individual cases the difference was occasionally 6 or 7 mm. In 37 per cent of this group, T was of the same positive amplitude in both precordial leads. Only twice did the amplitude of T in Lead IV F exceed that in IV R. When both Leads IV R and IV F possessed negative T waves, the depth of the inversion was equal in exactly half the records, but in the remainder, T was more deeply inverted in Lead IV R about three times as often as in Lead IV F. In summary, the T wave, whether positive or negative, tended to be a larger deflection in Lead IV R than in Lead IV F.

Q-T Duration.—Careful measurement of the Q-T duration in 115 unselected pairs of precordial leads yielded identical values after corrections were made for differences in heart rate. In this respect, therefore, Leads IV R and IV F appear to be identical.

SECTION II. COMPARISON OF DISSIMILAR LEADS IV R AND IV F, WITH PREDOMINANT ABNORMALITIES IN IV F

Sixty-four pairs of precordial leads exhibited greater discrepancies than those summarized in Section I. These dissimilarities concerned particularly the RS-T segments and T waves. In fifty-five of these records Lead IV F revealed abnormalities greater in degree and pathologic significance than were noted in IV R. This group is presented for convenience under several roughly etiologic subdivisions, as follows:

Coronary Thrombosis Group.—Eighteen patients with a diagnosis of coronary thrombosis had electrocardiograms in which Lead IV F gave clearer indication of the infarct than did Lead IV R. Samples of the precordial leads are given in Plates I and II, and the accompanying legends offer other electrocardiographic and clinical details.

In three patients with recent coronary thrombosis (Plate I, Figs. 1, 6, and 7), Lead IV R was entirely normal, while IV F was sufficiently abnormal to confirm the clinical diagnosis. It is to be noted, however, that in none of these records was the R wave lost, which is considered typical of thrombosis in the left coronary artery system,² nor were the standard leads typical of either anterior or posterior infarction. However, the outcome in the first case, and the clinical features and electrocardiographic developments in the other two, pointed to coronary thrombosis. The atypical electrocardiographic features may have resulted from an unusual location of the lesion.

All of the cases illustrated in Plate I, by Figs. 2, 3, 4, 5, 8, 11, and 12, presented earlier or more dramatic changes in Lead IV F than in IV R. In follow-up records on three of these patients the T-wave abnormalities developed more fully in Lead IV F, but failed to appear at all in Lead IV R (Plate I, Figs. 4, 6, and 7).

In five cases of coronary thrombosis which had occurred in the distant past, the lesion was more definitely revealed in Lead IV F than in IV R (Plate I, Figs. 8a, 9, 13, and 15; Plate II, Fig. 1). Particularly

interesting was the fact that, in a case in which changes typical of anterior and apical cardiac infarction had been portrayed equally well in both precordial leads until a month after the acute episode, Lead IV R had returned to normal four months later, whereas the T deflection was still negative in Lead IV F (Plate I, Figs. 14a and b).

Digitalis Group.—Nine of the patients who were under the influence of digitalis exhibited electrocardiograms in which the T deflection was positive in Lead IV R and negative in Lead IV F. Whether digitalis was the only, or chief, factor in the T-wave inversion is open to reasonable question, because hypertension was present in six of these subjects and, as will be seen below, negativity of T may occur in the precordial leads of such patients. However, the RS-T and T changes exhibited in Plate II, Figs. 4, 5, 7, 9, 10, and 11, are like those generally recognized in standard leads as of the "digitalis variety." Definite evidence that digitalis was a causative factor was found in subject J. B. (Plate II, Fig. 7). An electrocardiogram obtained one week prior to digitalization showed large, positive T waves in Lead IV F; following the administration of digitalis, T assumed the opposite direction here illustrated. Again, in subject J. T. (Plate II, Fig. 8), who had neither hypertension nor clinical evidence of coronary occlusion, but manifested digitalis intoxication with coupled rhythm, the fact that T was isoelectric in Lead IV F would appear to be explainable as an effect of digitalis.

Hypertension Group.—Hypertension of considerable degree or long duration has been known frequently to alter the direction of the T wave in the limb leads³ and precordial leads.⁴ Although inversion of the T wave in both of the precordial leads of patients with hypertension was commonly encountered in this study, there were eight subjects in whom the T deflection was positive in Lead IV R, but deeply inverted or, in two instances only, diphasic or isoelectric in Lead IV F. None of this group was receiving digitalis.

Miscellaneous Group.—Twelve instances of significant discrepancy between Leads IV R and IV F were encountered in five patients whose etiologic diagnoses differed from those considered above. Samples of their precordial electrocardiograms are illustrated in Plate III, Figs. 9 through 13, and the accompanying legends contain descriptive clinical notes. None of these subjects was receiving digitalis. It is remarkable that in only three of the many instances of arteriosclerotic heart disease uncomplicated by hypertension or coronary thrombosis included in this study were there significant differences between Leads IV R and IV F. They are depicted in Plate III, Figs. 11, 12, and 13.

The attempted etiologic grouping of the data in this section served chiefly the purpose of convenience. Some overlapping of cases in each category is readily acknowledged, and no deductions as to the respective value of these two precordial leads in relation to etiology should

PLATE I

Coronary Thrombosis Group.

Fig. 1.—G. S., male, 70 years old. Several long, severe attacks of coronary pain during week. No previous cardiac symptoms. *EKG*: Isoelectric T in Lead I, and deeply negative T in Lead IV F only. *Course*: Sudden death five days later in another severe attack.

Fig. 2.—D. A., female, 70 years old. Known to have had hypertension for five years. Sudden attack of cardiac asthma with fall in blood pressure, followed by progressive congestive failure with death ten weeks later. *EKG*: Prominent Q wave and negative T in Leads II and III; T positive in Lead IV R, but negative in IV F.

Fig. 3a and b.—N. F., male, 56 years old. Sudden, severe attack of typical coronary pain, with collapse, cyanosis, hypotension, and transient fever and leucocytosis. *EKG*, twenty-four hours after onset, showed only low voltage in Leads I, II, and III, with neither precordial lead typical of recent infarction (3a). Two days later standard leads still equivocal, but Lead IV F now typical (3b).

Fig. 4a and b.—I. B., female, 72 years of age. History of treated syphilis. Typical attack of coronary occlusion, with transient fever and leucocytosis. *EKG*, two days after onset, showed left axis deviation and negative T deflection in Leads I, II, and III; precordial leads indeterminate (not illustrated). Nine days later, T isoelectric in Lead IV F only (4a), and five days later T had become inverted in Lead IV F but not in IV R (4b).

Fig. 5a and b.—W. P., male, 42 years of age. Angina pectoris for five months. Unusually severe attack, ten days before admission, lasting four hours, accompanied by sweating, weakness, nausea, and fall in blood pressure; fever and leucocytosis transiently. *EKG*, ten days after onset, showed left axis deviation and "cove-plane" T-wave inversion in Lead I; Lead IV F far more typical of recent infarction than IV R (5a), but a week later both precordial leads equally abnormal (5b).

Fig. 6a and b.—L. E., female, 64 years old. Arteriosclerotic heart disease, with hypertension and moderate angina pectoris. Clinically typical acute coronary occlusion, with pericardial friction, fall in blood pressure, fever, leucocytosis. *EKG*, three days after onset, showed marked left axis deviation and diphasic T in Lead III; the latter became deeply negative six days later. Lead IV R normal throughout, but T in Lead IV F was probably abnormal in both records (6a and b). Tracing one week later identical with above.

Fig. 7a and b.—A. M., female, 73 years old. Serologic tests for syphilis were positive. Crushing chest pains with dyspnea and vomiting; transient fever and leucocytosis. *EKG*, two weeks after onset, showed low voltage, very low T waves in Leads I and II, normal Lead IV R, and a diphasic T in Lead IV F (7a). Eleven days later, T inverted in Lead I, isoelectric in Lead IV F, but Lead IV R still normal (7b).

Fig. 8a, b, and c.—J. P., female, 50 years of age. Known to have had hypertension with angina pectoris for three years. Typical left coronary artery thrombosis with classical serial electrocardiographic changes. Admitted to hospital because of chronic pyelitis. *EKG*, two years after known coronary thrombosis, showed marked left axis deviation and isoelectric T in Lead I. Precordial leads both abnormal, but IV F more characteristic of old infarct than IV R (8a). Six weeks later suffered another attack of coronary thrombosis. *EKG*, taken one and ten days after last episode, showed negative T in Lead I. Both precordial leads again markedly abnormal, but again Lead IV F showed greater changes (8b and c).

Fig. 9.—G. W., male, 60 years old. Alleged to have had a typical attack of coronary thrombosis at home eight months before; referred to laboratory for follow-up examination. *EKG*: Isoelectric T in Lead I, and negative T deflection in Lead IV F only.

Fig. 10.—R. F., female, 45 years old. Serologic tests for syphilis positive, acute rheumatic fever at 35, with recurrent congestive failure thereafter. Severe attacks of coronary pain for two weeks before admission. Physical signs of mitral and aortic stenosis. Transient fever and leucocytosis. *EKG*: Right axis deviation, and small, negative T deflections in Leads II and III. In Lead IV F the high RS-T segment level, negative T wave, and absence of the R wave were considered typical of recent myocardial infarction; Lead IV R less strikingly abnormal. *Course*: Temporary improvement, with recurrence of congestive failure and death two months later. *Necropsy*: Complete occlusion of anterior descending branch of left coronary artery, healed infarct at left apex, mitral and aortic rheumatic endocarditis with stenosis, pulmonary and splenic infarcts.

Fig. 11.—T. O., male, 52 years old. Exertional angina pectoris for two weeks, with a severe episode lasting four hours. *EKG*, four days later, showed isoelectric T in Lead I, and dissimilar precordial leads; the abnormalities in IV F seemed more clearly indicative of coronary thrombosis than those in IV R.

Fig. 12.—C. C., male, 49 years old. Clinically typical coronary thrombosis, with ensuing hypotension, leucocytosis, and pericardial friction. Progressive congestive failure led to death in one week. *EKG*, four days after onset, showed left axis deviation and negative T deflection in Lead I. Lead IV F much more strikingly typical of recent myocardial infarction than IV R.

(Legends continued on top of page 722.)

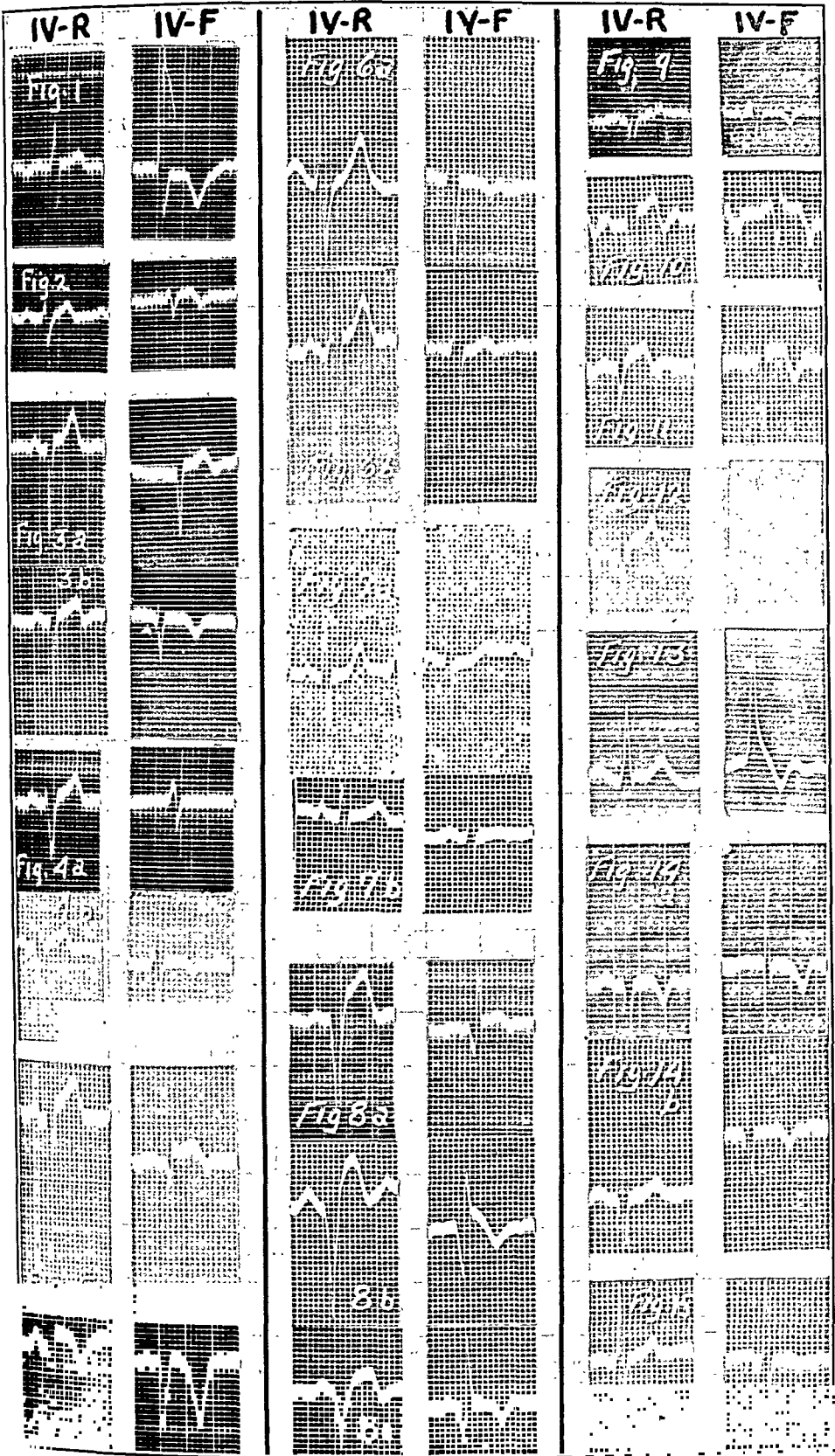


PLATE I
(See opposite page for legends.)

Fig. 13.—J. R., male, 60 years old. Hypertensive cardiovascular disease for twenty years. Apparently had coronary thrombosis eighteen months before admission, with angina pectoris thereafter. *EKG*: Incomplete A-V block, marked left axis deviation, and negative T deflections in Leads I and II. Precordial leads possibly distorted by artifact, but Lead IV R apparently normal, while in IV F the inversion of T is unmistakable.

Fig. 14a and b.—E. C., female, 67 years old. Arteriosclerotic heart disease with hypertension. Coronary thrombosis with electrocardiographic indications of anterior and apical infarction. *EKG*, one month after acute episode, showed persistent inversion of T in Leads I and II and both precordial leads (14a). Four months later, Lead IV R restored apparently to normal, while Lead IV F retained negative T deflection (14b).

Fig. 15.—J. C., male, 77 years old. Coronary thrombosis two years before, with typical electrocardiographic signs of apical and anterior infarction; angina pectoris subsequently. *EKG*, two years after acute episode, showed left axis deviation and diphasic T in Lead I. Lead IV R normal, while IV F still had negative T deflection.

PLATE II

Coronary Thrombosis Group (cont.)

Fig. 1.—J. C., female, 64 years old. Hypertension, and, probably, coronary thrombosis ten months before she was admitted to hospital for carcinoma of pleura. No evidence of pericardial metastases. *EKG* showed low voltage in standard leads, with small, positive T deflections. Of the precordial leads, only IV F showed a persistently abnormal T deflection.

Fig. 2a and b.—A. B., negro male, 54 years old. Severe angina pectoris for two years, with virtual invalidism. *EKG* showed shallow inversion of T in Leads II, III, and IV F, but not in IV R. Another tracing, three days later, taken to exclude possibility of technical error in obtaining the precordial leads, was identical with the first (2b).

Fig. 3a and b.—A. N., male, 67 years old. Arteriosclerotic heart disease, with hypertension and angina pectoris. Admitted for upper abdominal pain and chills. Roentgenograms disclosed filling defect in ascending colon, and displacement of kidney. Because of acute development of dyspnea, cyanosis, and pulmonary edema, patient was digitalized rapidly. *EKG*: Small T waves in Leads I and II. Lead IV R lacked an R wave, while Lead IV F showed deep inversion of T (3a). Two days later, T had turned downward in Lead IV R also (3b). *Course*: Sudden death one week later. Final diagnosis: questionable coronary thrombosis; carcinoma of colon.

Digitalis Group

Fig. 4.—W. V., male, 42 years old. Hypertensive heart disease and moderate congestive failure. Patient recently digitalized. *EKG*: Diphasic T wave in Leads II and III, and inversion of T in IV F but not in IV R.

Fig. 5a and b.—J. D., male, 51 years old. Arteriosclerotic heart disease with acute pulmonary edema. Digitalized, with prompt relief of symptoms. No hypertension. *EKG*: Typical digitalis-type T-wave inversion in Leads I and IV F, but not in IV R (5a). Tracing one month later showed similar, but less pronounced, abnormalities.

Fig. 6a, b, and c.—J. Q., male, 53 years of age. Arteriosclerotic heart disease with hypertension and moderate congestive failure. Patient fully digitalized. *EKG*: Three tracings in five days all showed left axis deviation and negative T deflections in Leads I and IV F only.

Fig. 7.—J. B., male, 58 years old. Arteriosclerotic heart disease with angina pectoris and mild congestive failure. Digitalized. *EKG*: Low voltage in standard leads, with almost isoelectric T in Lead I. T wave diphasic in Lead IV R, but definitely inverted in IV F.

Fig. 8.—I. A., female, 70 years old. Arteriosclerotic heart disease with hypertension and congestive failure. Digitalized. *EKG*: Auricular fibrillation, with isoelectric T waves in the standard leads and Lead IV F.

Fig. 9.—H. B., female, 32 years of age. "Malignant hypertension" with cardiac and renal failure led steadily to death in spite of digitalization. *EKG*: Left axis deviation. RS-T segment level slightly low in Lead I, but T waves positive in all leads except IV F, in which inversion of the digitalis type was present.

Fig. 10.—J. T., female, 74 years old. Arteriosclerotic heart disease with moderate congestive failure. Digitalis intoxication. *EKG*: Coupled rhythm, low T waves in Leads I and II. T was a positive deflection in Lead IV R, and negative in IV F. Note, also, opposite directions of T in the ectopic ventricular beats.

Fig. 11.—E. B., male, 58 years old. Arteriosclerotic heart disease, with hypertension and moderate congestive failure. Digitalized. *EKG*: left axis deviation, isoelectric T waves in Leads I, II, and III, and low RS-T segment level in Lead I. In Lead IV R the T wave was a positive deflection, while in Lead IV F it was negative.

Fig. 12.—F. B., male, 89 years old. Arteriosclerotic heart disease with hypertension and moderate congestive failure. Digitalized. *EKG*: Isoelectric T wave in Leads I, II, and IV F only.

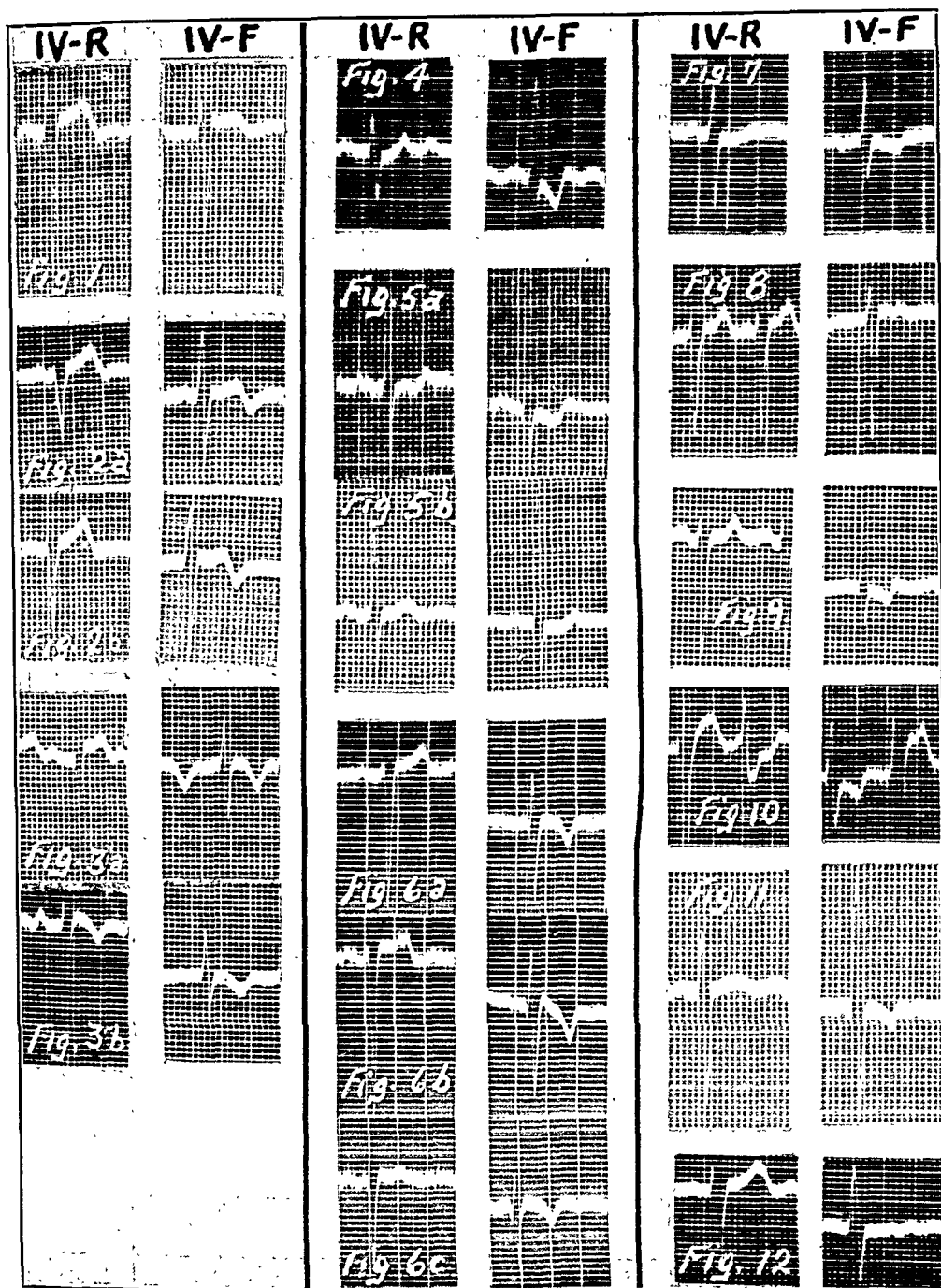


PLATE II

(See opposite page for legends.)

PLATE III

Hypertension Group

Fig. 1.—J. O., male, 40 years of age. Hypertensive cardiovascular disease, with subarachnoid hemorrhage. No digitalis. *EKG*: Marked left axis deviation, and negative T deflections in Leads I, II, and IV F, but not in IV R.

Fig. 2.—L. L., female, 51 years old. Severe hypertension, with mild congestive failure and cerebral symptoms. No digitalis. *EKG*: Marked left axis deviation, with negative T deflections in Leads I, II, and IV F; large positive T deflection in Lead IV R.

Fig. 3*a*, *b*, and *c*.—E. S., female, 61 years old. Arteriosclerotic heart disease and hypertension. *EKG*: Left axis deviation; negative T deflections in Leads I and IV F; large, positive T deflection in IV R (3*a*). Tracings repeated twice in week to rule out technical error, but records similar (3*b* and *c*).

Fig. 4.—J. T., female, 27 years old. Cushing's syndrome of pituitary basophilism, including hypertension. *EKG*: Left axis deviation, negative T deflection in Leads I and IV F only. Similar tracings eleven weeks later.

Fig. 5.—G. K., male, 85 years old. Arteriosclerosis and hypertension. No heart failure; patient not digitalized. *EKG*: Left axis deviation. T deflections in all leads, except IV F, were positive.

Fig. 6.—G. K., female, 54 years old. Hypertension and anxiety state. Possibly had coronary thrombosis eight months before. *EKG*: Marked left axis deviation, with negative T deflections in Leads I and II. Both precordial leads abnormal, but in IV R the T wave was isoelectric, while in IV F it was deeply inverted.

Fig. 7.—H. H., female, 40 years old. Obesity, with hypertension, and, probably, angina pectoris. No digitalis. *EKG*: Left axis deviation, diphasic T wave in Lead I. In Lead IV R the T wave was positive, while in IV F it was negative.

Fig. 8.—M. K., male, 75 years old. Arteriosclerotic heart disease with hypertension and congestive failure. *EKG*: Record obtained before digitalization showed normal T deflections in all leads except IV F. Following digitalization T became a negative deflection in all leads. *Course*: Congestive failure progressed in spite of digitalis and other treatment, and patient expired three weeks later.

Miscellaneous Group

Fig. 9.—C. L., male, 17 years old. Acute rheumatic pancarditis. No digitalis. *EKG*: T deflections small and inverted in Leads I, II, and IV F; T deflection small, but positive, in Lead IV R. In several other tracings taken during next three months the precordial leads remained much the same as those here illustrated; Lead IV R was always border-line with respect to the character of its T wave, while in IV F it was clearly abnormal in being consistently negative.

Fig. 10.—J. A., male, 58 years old. Arteriosclerotic heart disease with moderately severe angina pectoris. Digitalis discontinued three weeks before admission. *EKG*: T waves small, but upright in standard leads. Lead IV R perfectly normal, but in IV F the T deflection was deeply negative.

Fig. 11.—R. P., female, 72 years old. Arteriosclerotic heart disease, with, possibly, thiamin deficiency, and congestive failure. No digitalis. *EKG*: Left axis deviation, QRS slurring, and small, but positively directed, T waves in standard leads. T in Lead IV R appeared normal, while in IV F it was practically isoelectric. Five subsequent records in the course of several weeks were essentially the same, with persistent inconsistency in the precordial leads. *Course*: No clinical improvement with thiamin chloride administration, but recovery after digitalization.

Fig. 12.—C. R., male, 55 years of age. Rheumatic aortic stenosis, with syncopal attacks. No digitalis. *EKG*: Left axis deviation, with diphasic T waves in Leads I, II, and IV F, but a normal Lead IV R.

Fig. 13.—G. G., male, 54 years old. Arteriosclerotic heart disease with diabetes mellitus. No digitalis. *EKG*: Isoelectric T deflections in Leads I and IV R; however, in Lead IV F the T deflection was definitely negative.

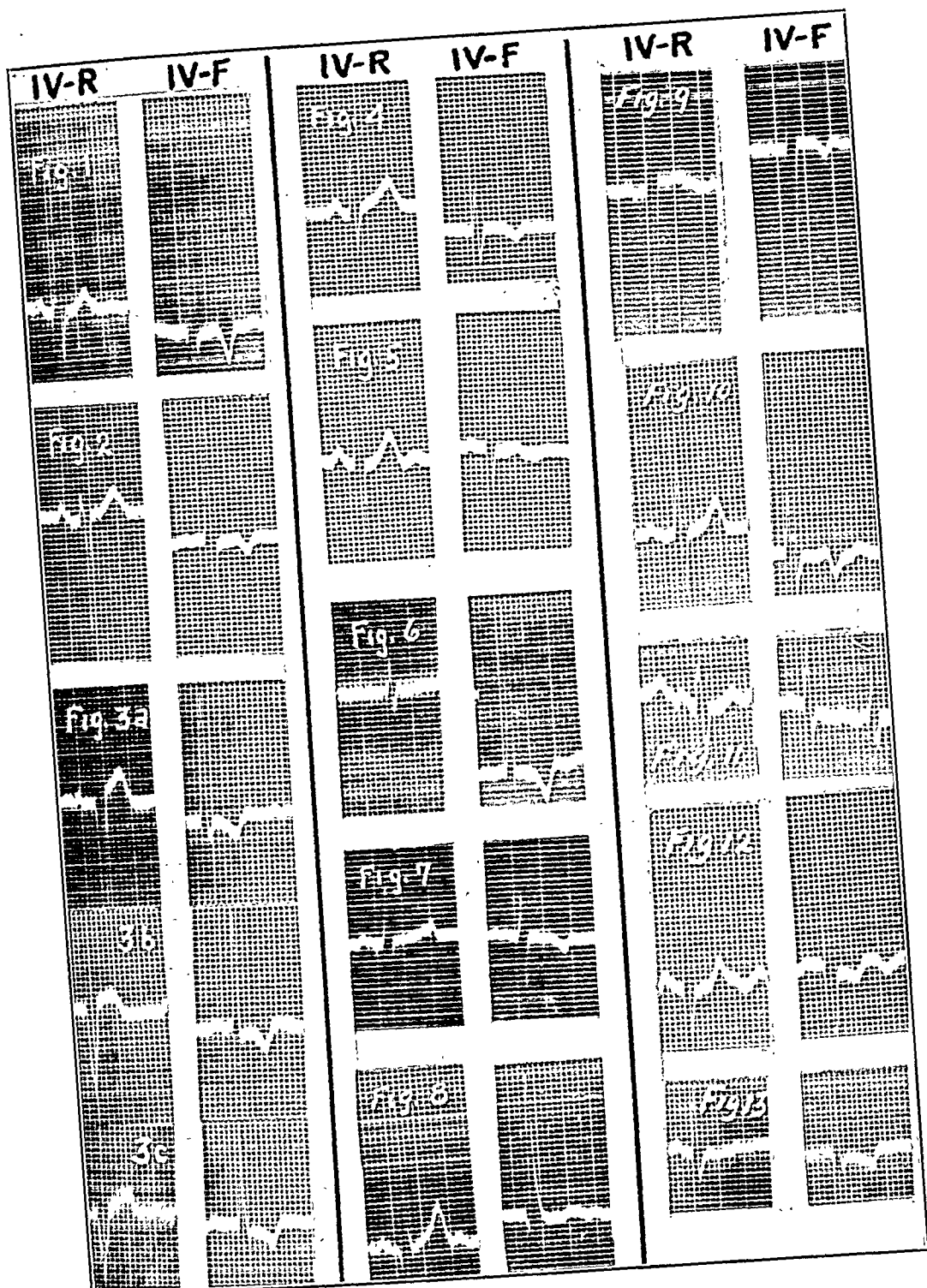


PLATE III

(See opposite page for legends.)

be ventured on so few data. The point that justifies emphasis is that Lead IV F may occasionally reveal significant abnormalities which are absent from, or less clearly presented in, Lead IV R.

SECTION III. PRESENTATION OF DISSIMILAR LEADS IV R AND IV F WITH PREDOMINANT ABNORMALITY IN LEAD IV R

In only nine instances (2.3 per cent), and from but four patients (1 per cent), were more definite abnormalities encountered in Lead IV R than in Lead IV F (Plate IV). In two of the patients coronary thrombosis had apparently occurred, and, although in both instances Lead IV F showed abnormalities of the T waves which might have confirmed the clinical impression, significant changes were more fully portrayed in Lead IV R of the earlier records (Figs. 1 and 2). Fig. 4 illustrates discrepancies in the precordial leads which were found in a case of probable vitamin B deficiency and cardiac failure. The T deflections were negative in Lead IV R, and positive in IV F. The greater abnormality of Lead IV R as compared with IV F, as shown in Fig. 3a, is of uncertain significance, and one cannot say in this case which lead gave more accurate information.

Apparently it is rare for Lead IV R to show greater abnormalities than Lead IV F, but even these few observations indicate that the possibility of such an occurrence must be recognized. However, discrepancies between these two precordial leads are revealed in the vast majority of instances (86 per cent) by greater abnormality in Lead IV F than in IV R.

PLATE IV

Fig. 1a and b.—A. S., male, 53 years old. Angina pectoris for eight years. Two recent, unusually severe and persistent attacks, associated with vomiting and collapse, followed by transient fever and leucocytosis. *EKG*, two days after onset (1a), indicated coronary thrombosis more clearly in Lead IV R than in IV F. Tracing fifteen days later showed abnormalities of equal degree in the two precordial leads (1b).

Fig. 2a and b.—R. H., male, 50 years old. Brief syncopal attack, followed by a questionable pericardial friction. *EKG*, two weeks later, suggestive of coronary thrombosis, with T-wave abnormality more fully developed in Lead IV R than in IV F (2a). Tracing six months later (2b) showed marked regression of T-wave abnormality in all leads, but QRS in Lead IV R more clearly indicative of old cardiac infarct. Course: Sudden death two weeks later.

Fig. 3a and b.—G. A., male, 61 years old. Acute epigastric and substernal pain, followed by obstructive jaundice and epigastric tenderness. Slight transient fever and leucocytosis; convalescence uneventful. *EKG*: two records in one week showed intraventricular block and changes of uncertain significance; Lead IV R in 3a more strikingly abnormal than IV F, but doubt about the diagnosis prevented any decision as to which lead gave more accurate information.

Fig. 4a, b, and c.—L. C., male, 52 years old. Arteriosclerotic heart disease with auricular fibrillation, and progressive congestive failure for eight months in spite of theoretically adequate digitalis medication. Diet considered deficient in vitamin B. Patient exhibited generalized anasarca and frank peripheral neuritis. Venous pressure 21 cm. water, arm-to-tongue circulation time 19 sec. Digitalis stopped because of marked bradycardia. Thiamin chloride and nicotinic acid given in large doses, mercurial diuretic given intravenously once; eliminated 15 pounds of edema fluid, and peripheral neuritis cleared up. *EKG*: Three records during first ten hospital days showing discrepancy in direction of T in precordial leads. Fourth record, three weeks later, not illustrated, showed positive T deflections in all leads. Final diagnosis: heart failure questionably related to vitamin B deficiency.

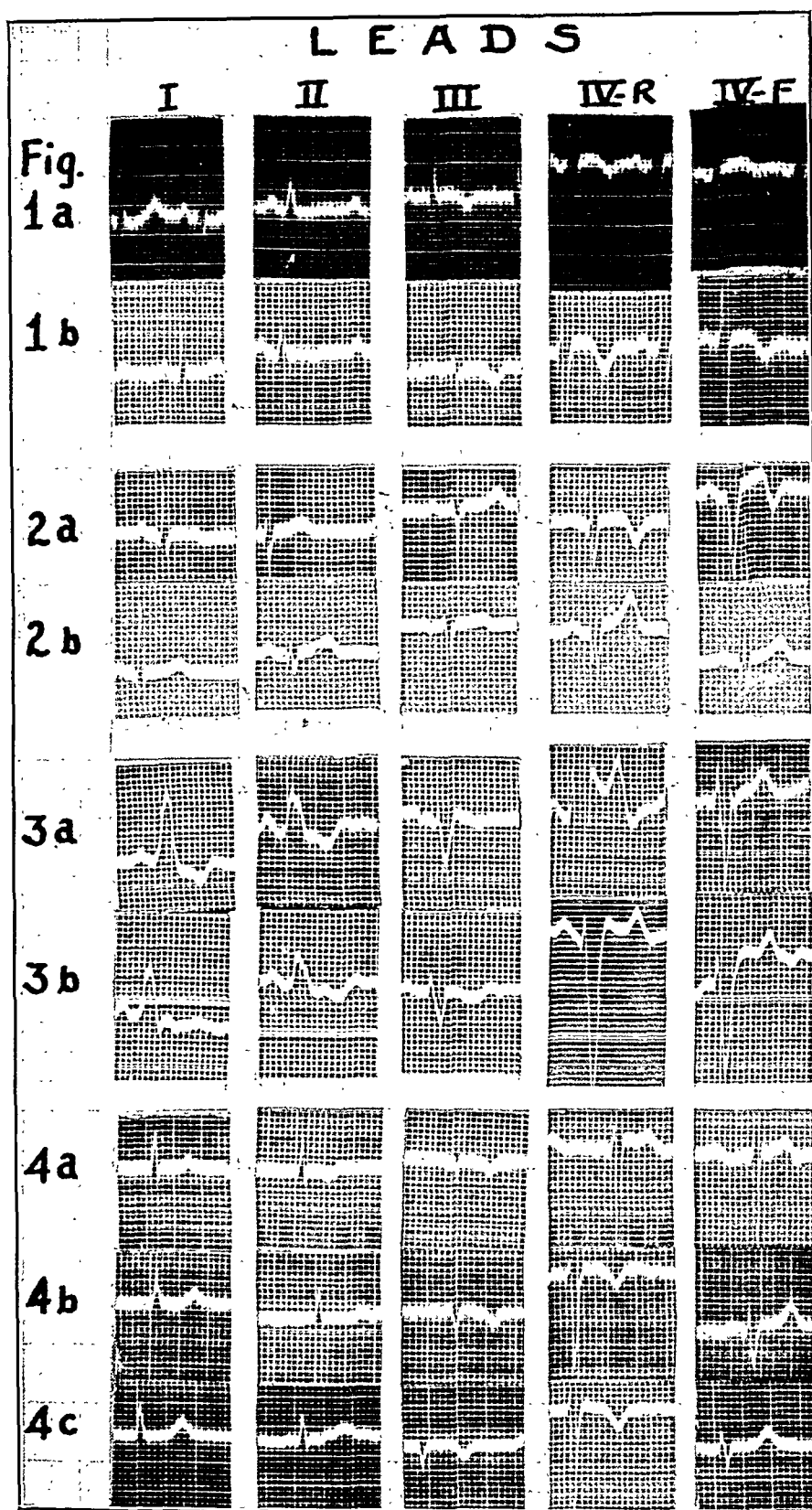


PLATE IV
(See opposite page for legends.)

SUMMARY

Leads IV R and IV F were studied in 400 electrocardiographic examinations of 349 patients known to have, or suspected of having, heart disease.

Although 84 per cent of the precordial leads were considered as being essentially the same, the following minor differences were noted in the two groups: Lead IV F was inferior to IV R in depicting the P wave and P-R interval. QRS in Lead IV F tended more often to be a positively directed complex, but was smaller in amplitude than in Lead IV R. The level of the RS-T junction was less often elevated (positive) in Lead IV F than in IV R. The T wave, whether positive or negative, was, on the average, smaller in amplitude in Lead IV F than in IV R. The Q-T duration was identical in the two leads.

Sixty-four pairs (16 per cent) of the records exhibited significant discrepancies, particularly in the RS-T portions and T waves. In fifty-five of these instances, the abnormalities occurred either alone in Lead IV F, or to a significantly greater degree in Lead IV F than in Lead IV R. Illustrations of all of the dissimilar precordial electrocardiograms are shown in the plates, and brief clinical notes are presented in the accompanying legends.

CONCLUSION

Lead IV F is definitely superior to IV R in the detection of cardiac abnormalities, and it should be given preference in routine clinical electrocardiographic examinations.

REFERENCES

1. Standardization of Precordial Leads; Joint Recommendations of the American Heart Association and the Cardiac Society of Great Britain and Ireland, *AM. HEART J.* 15: 105, 1938. Supplementary Report, *AM. HEART J.* 15: 235, 1938.
2. Ashman, R., and Hull, E.: *Essentials of Electrocardiography*, New York, 1937, The Macmillan Co.
3. Rykert, H. E., and Hepburn, J.: *Electrocardiographic Abnormalities Characteristic of Certain Cases of Arterial Hypertension*, *AM. HEART J.* 10: 942, 1935.
4. Van Nieuwenhuizen, C. L. C., and Hartog, H. A. Ph.: *The Electrocardiogram in Hypertension with Special Reference to Lead IV*, *AM. HEART J.* 13: 308, 1937.

ROENTGENKYMOGRAPHY OF THE HEART

ITS CLINICAL APPLICATIONS AND LIMITATIONS

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THE application of roentgenologic methods to the study of the heart has proved an invaluable adjunct to clinical examination. Roentgenograms give a permanent record of the size, shape, and position, and under controlled conditions permit reasonably accurate measurements of the heart shadow. Fluoroscopy, by visualizing the movements of the heart, has afforded the opportunity to study its functional status, in addition to its morphologic variations. This method of examination gives information only to the individual observer, and its value depends upon the experience and skill of the one making the examination. The advent of roentgenkymography has provided a simple technique for graphically recording the movements of the heart on a single film. A permanent record of the motion is thereby obtained, which, upon closer inspection, reveals details of movements which are difficult or impossible to see with the poor illumination and speed of motion that obtain during fluoroscopic examination.

Increasing experience with this mode of study, considered in the light of the accumulated literature, now makes it possible to estimate its sphere of clinical usefulness as well as to recognize that it has certain definite limitations. The material for this report comprises the roentgenkymograms of 350 normal subjects of various ages, and those of a large number of patients with heart disease.‡ A list of selected references to the pertinent literature is appended.

The principle of roentgenkymography is very simple; it is illustrated in Fig. 1. If a lead shield with a thin horizontal slit is interposed between the subject and the sensitized film, the only part of the heart shadow registered on the film is the thin horizontal segment opposite the slit. If the film is moved downward during a continuous x-ray exposure, the pulsating movements of the two points visualized at corresponding levels on the two sides of the cardiac contour will be recorded

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Received for publication June 21, 1939.

‡The normal kymograms were taken in the diagnostic laboratory of the Equitable Life Assurance Society of the United States. The majority of the patients were studied at Kings County Hospital. The authors wish to acknowledge with thanks the cooperation of the x-ray department of Kings County Hospital, under the directorship of Dr. Richard Rendich; and are particularly obliged to Dr. Gilbert Alexander, who constructed the kymographic apparatus at Kings County Hospital and collaborated in the early phase of the study. Mr. Russell Stamm, of the x-ray laboratory of the Equitable Life Assurance Society, rendered valuable technical assistance.

on the moving film in the form of a wave, and the waves will be repeated with each cardiac cycle (Fig. 1).

This ingenious technique was first described by Sabat,¹ in 1911, but was almost entirely neglected for many years. The failing of the single-slit grid was that only two points of the cardiac contour were visualized. Stumpf² remedied this shortcoming and broadened the clinical applications of kymography by constructing a grid with multiple horizontal slits, making it possible to register numerous points along the cardiac contour simultaneously. With the multiple-slit grid the film must be moved only just a little less than the distance between two slits in order to prevent overlapping of the waves of adjacent segments. The type of grid most commonly employed has slits 0.4 mm. wide, spaced at 12 mm. intervals. The film is moved downward a little less than 12 mm. during a continuous exposure of one to two seconds, with respiration suspended in the phase of moderate inspiration. Thus, depending on the heart rate and duration of exposure, one to three complete cardiac cycles are generally recorded (Fig. 2). Since the film moves down during the exposure, the time ordinate is directed upward, i.e., the beginning of exposure is at the lower margin of a segment, the end of exposure above. For details of the technique the reader is referred to the articles of Hirsch.^{3a, b}

The roentgenkymograph may be obtained commercially or can be built at relatively small expense.^{4, 5} While the technique described is the one most generally employed, there are many variations. Thus, the grid may be moved and the film held stationary during the exposure, instead of moving the film as described above. The type of kymogram obtained with this method is illustrated in Fig. 3. Although the other thoracic structures appear in their normal configuration with this technique, the moving-film kymogram is usually preferable because it more closely portrays the movements of single points along the cardiac contour. Other types of grids have been employed. The grid devised by Cignolini⁶ permits registration of a greater number of cardiac cycles than is possible with the multiple-slit grid, and therefore is preferable when a prolonged exposure is desired, as in the study of arrhythmias. In addition to the movements at the border which are recorded by the kymogram, there are density changes in the heart shadow during the cardiac cycle. These are usually visible grossly, but may be analyzed in greater detail with the densograph devised by Stumpf.⁷

The kymogram of a normal subject is illustrated in Fig. 2. The waves of each chamber are characteristic. The ventricular wave consists fundamentally of a slow, bent, outwardly directed limb representing diastolic filling, succeeded by a sharp inthrust representing systolic ejection. The peaks of the waves therefore represent maximum diastole, and the troughs represent maximum systole. By connecting the peaks and troughs of adjacent segments in the manner illustrated in Fig. 4, one can obtain the outline of the ventricle in systole and in diastole. The

aortic wave shows a sharp outthrust synchronous with ventricular systole, and this is succeeded by a slow recession of the wave during diastole, interrupted by the aortic incisura. The auricular waves consist of multiple small serrations.

All of the segments are comparable in time because all of them are taken during the same exposure. The waves of the different chambers, therefore, may be graphically correlated on a time axis, and the sequence of events throughout the cardiac cycle can be carefully analyzed. Fig. 5 shows a graphic analysis of the various waves on a time axis,

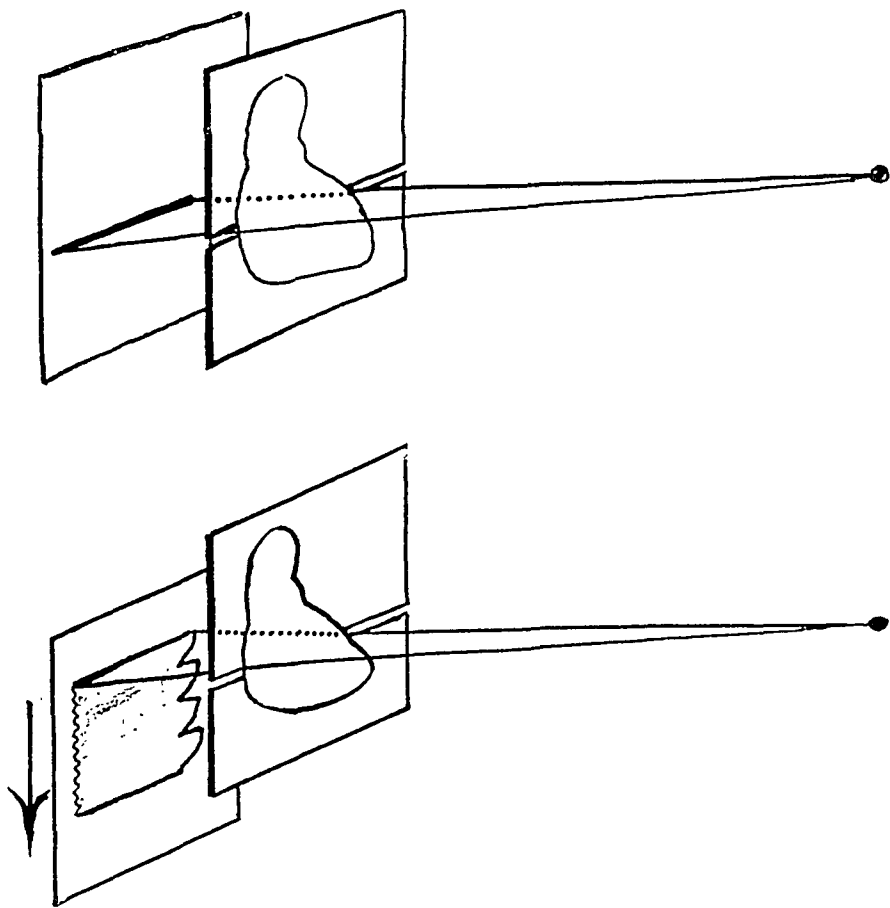


Fig. 1.—Principle of Slit Kymography. A lead shield with a thin, horizontal slit is interposed between the subject and the film, permitting only a narrow segment of the heart shadow, corresponding to the width of the slit, to be registered on the film. If the film is moved downward at a uniform rate during a continuous x-ray exposure, the pulsations of the two opposite points of the cardiac contour visualized will be recorded on the moving film in the form of waves, the waves being repeated with each cardiac cycle.

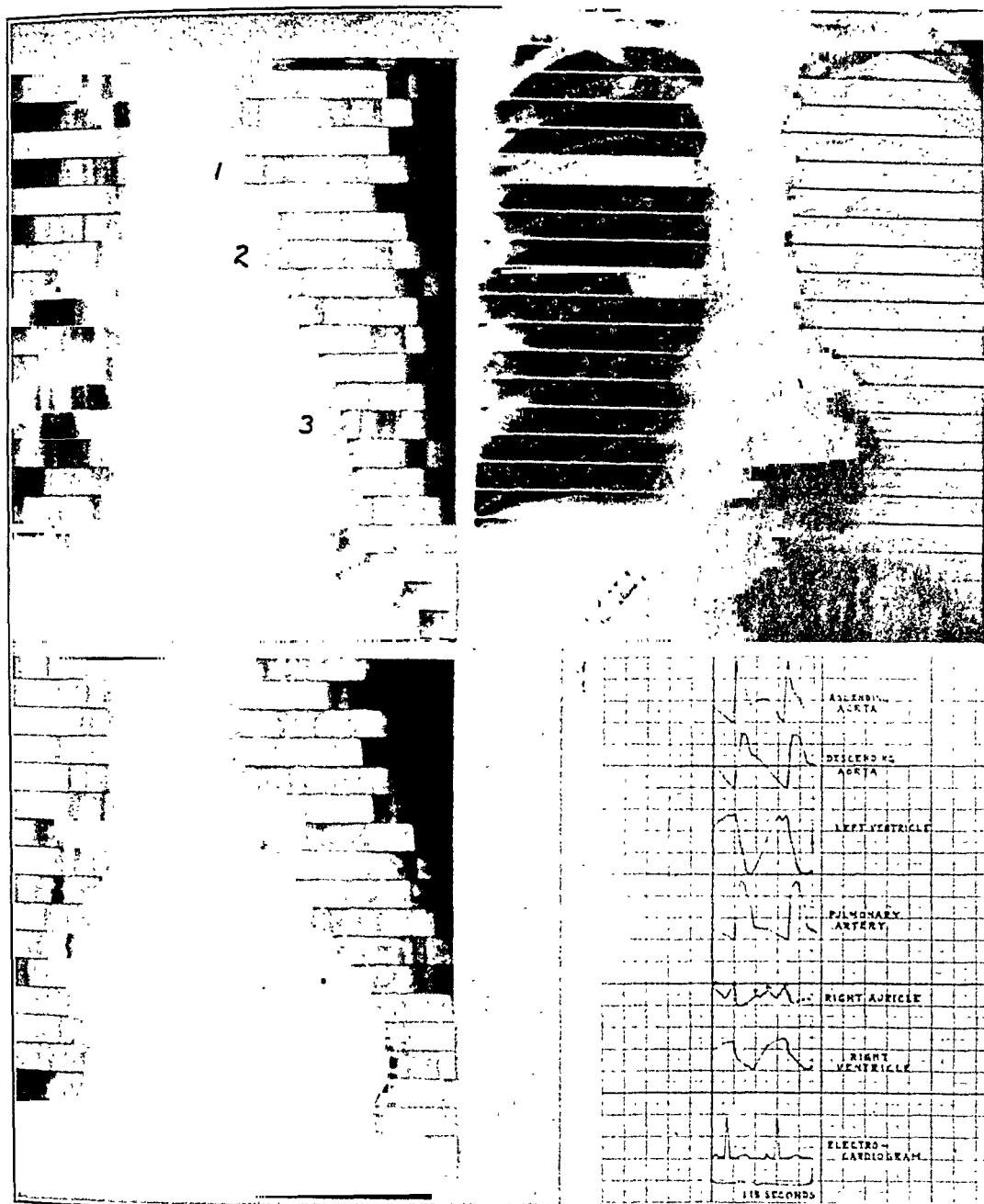
together with a simultaneously recorded electrocardiogram. By correlation with the electrocardiogram and heart sound records, the waves may be assigned to specific events in the cardiac cycle.^{3, 8} The phenomena recorded kymographically are readily susceptible of physiologic interpretation. The ventricular wave corresponds roughly to experimental ventricular volume curves. The waves of the aorta and pulmonary artery are identical with arterial sphygmograms. The auricular

waves frequently show three small serrations which correspond to the a, c, and v waves of the jugular pulse.

An interesting application of kymography has been an attempt at topographical analysis of the chambers composing the borders of the cardiovascular silhouette. The infrequent occurrence of aortic waves over the upper right heart border indicates that the vena cava rather than the ascending aorta usually forms this part of the cardiovascular shadow. The presence of ventricular waves over the lower right border has suggested that the right ventricle enters into the formation of the right heart border, contrary to usual belief. While this is probably true of vertically placed hearts, there is a legitimate criticism against accepting the occurrence of ventricular waves over the lower right cardiac contour as indicative of right ventricular movement. The movements of the right heart border are probably appreciably influenced by the left ventricle. In general, the waves along the right heart border in the posteroanterior views are very variable and of little clinical importance. The auricular waves are of little value, for those produced by the right auricle are ordinarily too small to be of any practical significance, while the left auricle contributes only a small and inconstant segment to the left cardiac border in the posteroanterior view.

The left ventricular and vascular (aorta and pulmonary artery) waves are more constant, and undergo interesting modifications in disease. Changes occur in time relationships, form, and amplitude. The interpretation of changes in amplitude is less certain than analysis of time relationships, which may be accurately resolved within 0.02 to 0.03 second. Although Johnson⁹ has found close correspondence between the amplitude of the left ventricular wave and the systolic output, the change in cardiac contour which the kymogram records is not purely a volume change, but is a resultant of the predominant contractile thrust, of rotary motion, and of positional changes of the heart as a whole. Furthermore, movement which is not parallel to the horizontal slit is distorted and magnified, as is evident in the upper ventricular frames of Fig 4. This distortion may, however, be easily corrected for in the manner illustrated.

The greatest objection to any quantitative interpretation of the kymographic waves is that, until now, kymograms have generally been taken at a distance of about 30 inches. Because of magnification of the image resulting from the short focal distance, no valid conclusions concerning heart size and its changes could be drawn. Teleoroentgenographic distance has not been attained hitherto because of the inability of ordinary Roentgen tubes to withstand the high exposure power required for kymography at the greater distance. Teleoroentgenographic distance has been made possible in our studies by the use of a tube of sufficiently high capacity, energized by a three-phase generator, which tends to maintain an almost even potential near peak value. One hundred eighty Ma. seconds at 60 to 85 kv., depending on the thickness of the chest and the



Fig

Fig

Fig. 2.—Roentgenkymogram of a normal subject.

Fig. 3.—Roentgenkymogram with moving grid and stationary film. The other thoracic structures appear in their normal relationships, in contrast to their segmented appearance in the moving film kymogram. This type of kymogram is not as satisfactory as the moving film kymogram, since it less accurately portrays the movement of single points of the heart.

Fig. 4.—Outline of the left ventricle in systole and in diastole. The peaks and troughs of each segment are projected to the same horizontal level before connecting them to obtain the outline of the ventricle in systole and in diastole. The kymogram records only that component of movement which is parallel to the slit, and the movement of the upper left ventricular contour is distorted and magnified because of the obliquity of this portion of the heart border. By connecting the peaks and troughs in the manner illustrated this factor is corrected, and the true amplitude of motion along the entire heart border is obtained.

Fig. 5.—Graphic correlation of the kymographic waves of various chambers in a normal subject, with a simultaneously recorded electrocardiogram. (Reprinted from Hirsch and Gubner, AM. HEART J. 12: 413, 1936.)

obliquity of exposure, were employed for a 1 to 1.5 second exposure. The measurements of the telekymogram correspond precisely to those of the regular teleoroentgenogram, and the telekymogram thus provides an accurate image of the heart and its movements. Telekymographic technique has been used by the authors in an attempt to obtain information concerning heart volume, cardiac output, and aortic elasticity.¹⁰ For ordinary clinical purposes, however, when quantitative values are unnecessary, the 30-inch kymogram, which requires only ordinary equipment, serves adequately.*

MYOCARDIAL INFARCTS

The most important clinical application of kymography is in the demonstration of myocardial infarcts. Ordinary roentgenologic examination is of little value in myocardial disease except when it indicates cardiac enlargement, or when in an occasional case it demonstrates aneurysm of the left ventricle secondary to myocardial infarction. Although isolated case reports have appeared illustrating changes in contraction in areas of myocardial infarction,^{11, 12} the value of kymographic examination in cases of coronary artery disease is not yet generally appreciated. In a study of forty-five cases of myocardial infarction the authors found definite kymographic changes in forty-one.¹³ Exposures were made in the posteroanterior and in two left oblique positions (about 25° and 60°), thus visualizing the movements of the anterior and posterior walls of the left ventricle. A fairly close correspondence was found between the electrocardiographic and kymographic localization of the infarct in those cases in which electrocardiographic localization was possible. The kymogram was found to be valuable for localizing and determining the extent of infarction following acute coronary artery thrombosis. In addition, kymographic examination frequently aided in the appraisal of the extent of myocardial damage in patients with angina pectoris, and in subjects with a history suggestive of previous coronary thrombosis.

Infarcted areas appear in the kymogram as localized segments which exhibit abnormal pulsations. Most commonly, partial or complete paradoxical pulsation is observed. While the remainder of the ventricle contracts normally, the infarcted region expands passively, instead of contracting, at the onset of systole, and collapses at the end of systole. Other types of movement are also observed in myocardial infarction. A double systolic pulsation or multiple bizarre movements during systole may occasionally occur. Marked diminution of the amplitude of the ventricular wave may occur in other conditions, but a localized impairment of contraction with normal motion in adjacent segments is highly suggestive of myocardial disease. It is difficult to explain why in one case reversal occurs, whereas in another there is only impaired contraction;

*Teleoroentgenographic technique was employed for the films taken at the laboratory of the Equitable Life Assurance Society. The roentgenkymograms made at the Kings County Hospital were taken at 30-inch distance.

of the ventricle is not more commonly diagnosed by roentgenologic examination.

The systolic distention of ventricular aneurysms is illustrated clearly in Fig. 8 *B*, taken from a patient who had sustained several attacks of

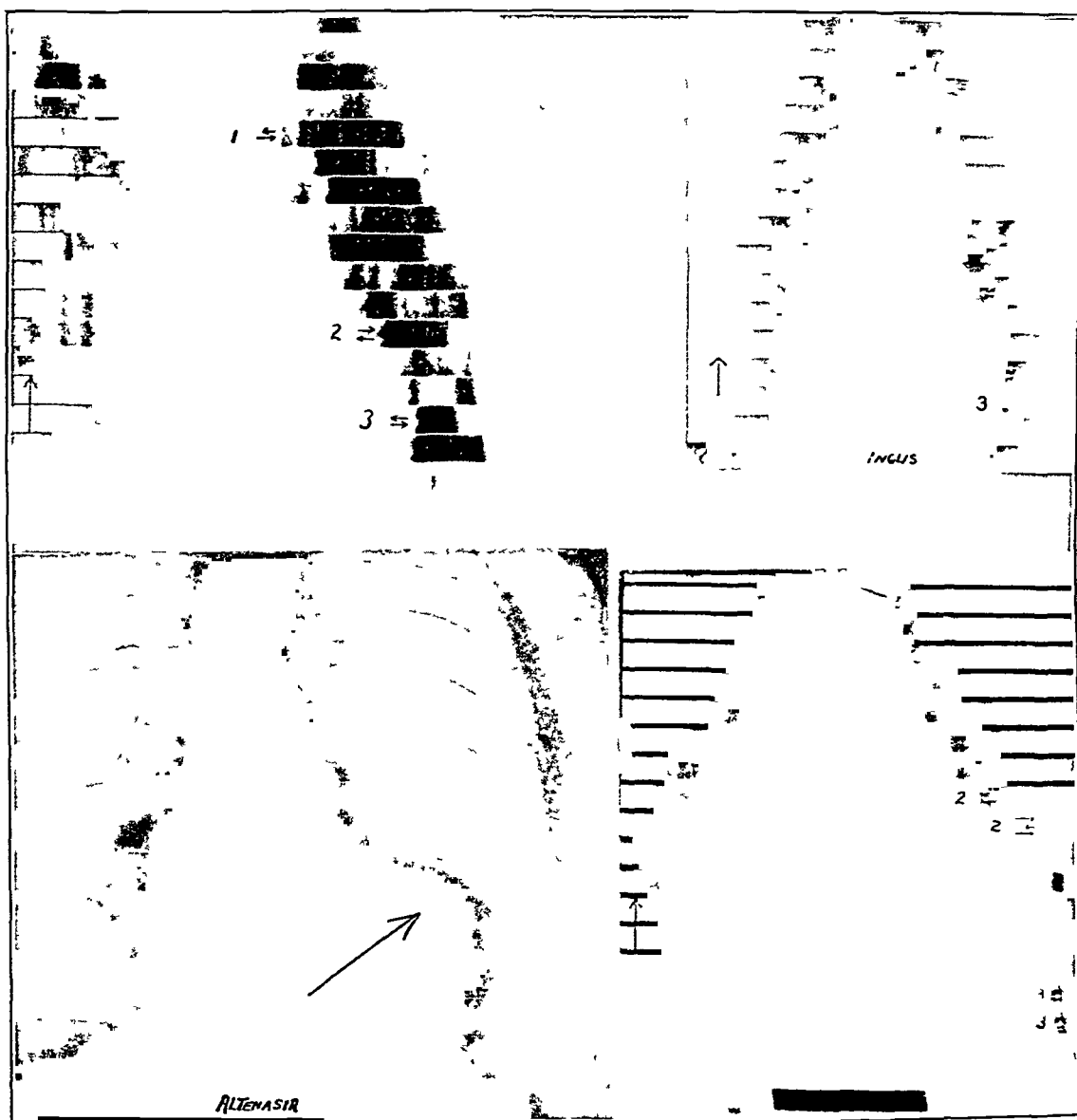


Fig. 6.—Myocardial Infarction. While the remainder of the ventricle contracts normally (2), the infarcted area (3) expands passively at the onset of systole instead of contracting, and collapses at the end of systole.

Fig. 7.—Roentgenkymogram of a patient with angina pectoris but without a history of coronary thrombosis and with a normal electrocardiogram. There is a definite reversal of pulsation of the apical and supra-apical region of the left ventricle, demonstrating an area of infarction.

Fig. 8.—*A*, Ventricular aneurysm. *B*, Roentgenkymogram shows systolic expansion of the aneurysmal sac, 2.

coronary occlusion. During systole the aneurysm balloons out as a passive sac, just as the aorta expands, and collapses at the end of systole when the fall of intraventricular pressure relieves the tension on the aneurysmal area. Scott and Moore¹⁵ have recently reported a case in which ordinary roentgenologic examination pointed to aneurysm of the ventricle, and the

kymogram showed paradoxical pulsation. At autopsy a highly malignant tumor, arising from the endothelium of the pericardium, was found. The underlying myocardium was invaded by the growth, and the destruction of the myocardium probably accounted for the paradoxical pulsation. We have observed the same roentgenographic and kymographic phenomena in a 13-year-old negress.

CARDIAC DECOMPENSATION

Marked enlargement of the heart, with cardiac decompensation, is generally accompanied by diminished amplitude of the ventricular pulsations, except in the case of aortic regurgitation. The movement of the apex is particularly reduced and may be absent or even reversed. This is due to impaired contraction of the ventricle as a whole, and to diminution or loss of the normal, upward, apical thrust. Furthermore, as Kirch¹⁶ has emphasized, the apex is the most labile portion of the ventricle; atrophy and thinning of the apex, with consequent loss of contractility, occur whenever there is cardiac enlargement with failure, regardless of the cause of the failure. Impaired, absent, and even reverse, movement in the apical region must therefore be interpreted with great caution, in so far as the possibility of localized myocardial disease is concerned, when there is any considerable degree of cardiac enlargement.¹⁷

PERICARDIAL EFFUSION

The movements are markedly diminished, or almost absent, over the entire heart border in cases of pericardial effusion (Fig. 9 A). On occasion, from the kymogram alone, it may be difficult to distinguish pericardial effusion from the markedly diminished pulsations seen in cardiac decompensation with marked enlargement of the heart. After resorption or paracentesis, the amplitude of the ventricular wave tends to return to normal (Fig. 9 B).

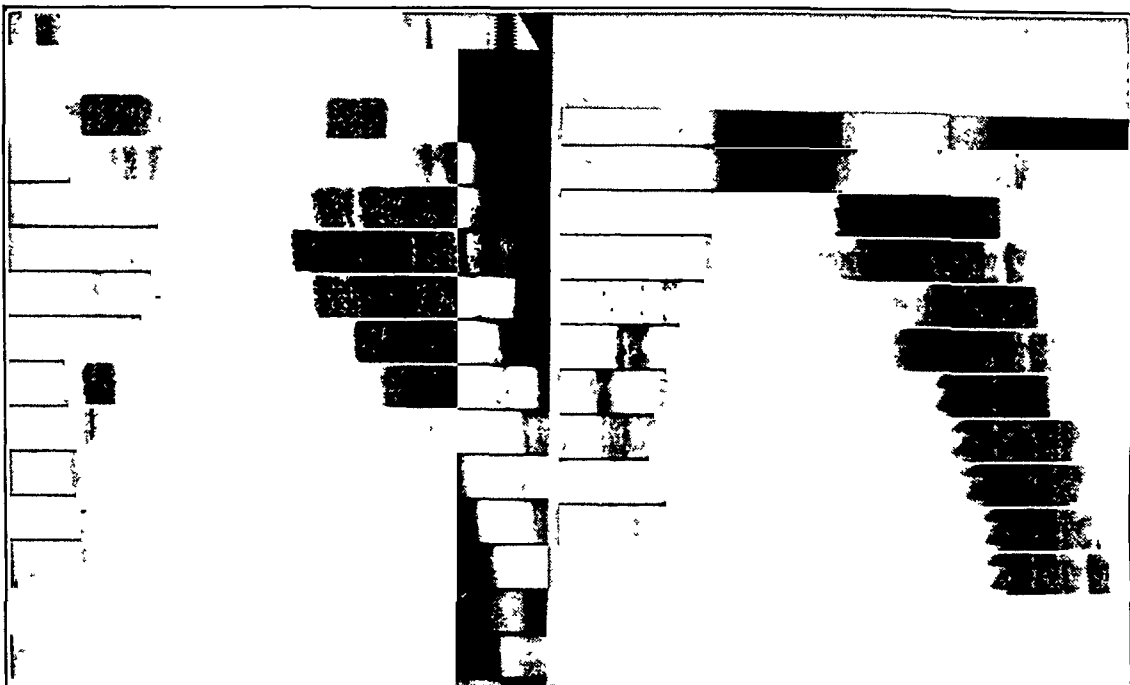
CONSTRICTIVE PERICARDITIS

Although the interpretation of diminution or absence of movement in cases of cardiac enlargement must be cautious, a generalized absence of movement when the heart is not enlarged is characteristic of concretion cordis, in which case the excursions are limited by the constricting pericardium. Fig. 10 illustrates a case of constrictive pericarditis in which the kymogram aided in the diagnosis. A pericardiectomy was performed, with complete relief of symptoms. Johnson⁴ reported a similar case and stressed the diagnostic value of roentgenkymography in this condition.

VALVULAR LESIONS

Characteristic changes in the ventricular and vascular waves may occur when valvular lesions are present. These have been reported in detail elsewhere.⁸

In *mitral insufficiency* the pressure in the left auricle is increased markedly during ventricular systole because of the regurgitation. The rate of inflow into the ventricle in early diastole is accordingly accelerated, and there is practically complete filling in the early inflow phase. Under these circumstances the ventricular wave may assume a trapezoid appearance. Occasionally, when the regurgitation is marked,



A.

B.

Fig. 9.—Pericardial Effusion: A, Roentgenkymogram shows generalized diminution of pulsation. B, Roentgenkymogram of same subject one month later, showing return of normal pulsations with resorption of the effusion. Reproduced through kind permission of Dr. Marcy Sussman, Roentgenologist of the Mount Sinai Hospital, New York City.

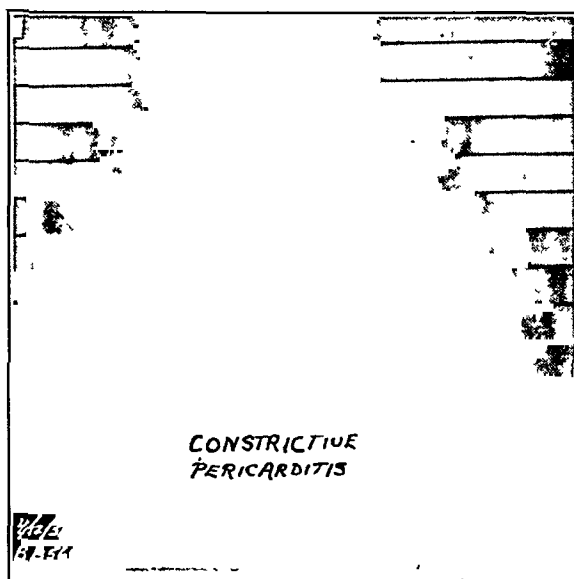


Fig. 10.—Constrictive pericarditis. There is a marked generalized impairment of contraction; heart of normal size.

a definite regurgitant wave may be seen in the auricle. Fig. 11 *B* shows filling of the auricle at the onset of systole in a case of advanced mitral valvular disease in which the enlarged left auricle formed the right heart border (Fig. 11 *A*).

In *mitral stenosis* the ventricular wave may be of low amplitude, and when the degree of stenosis is marked the filling of the ventricle in diastole is retarded, which is in contrast to mitral insufficiency.

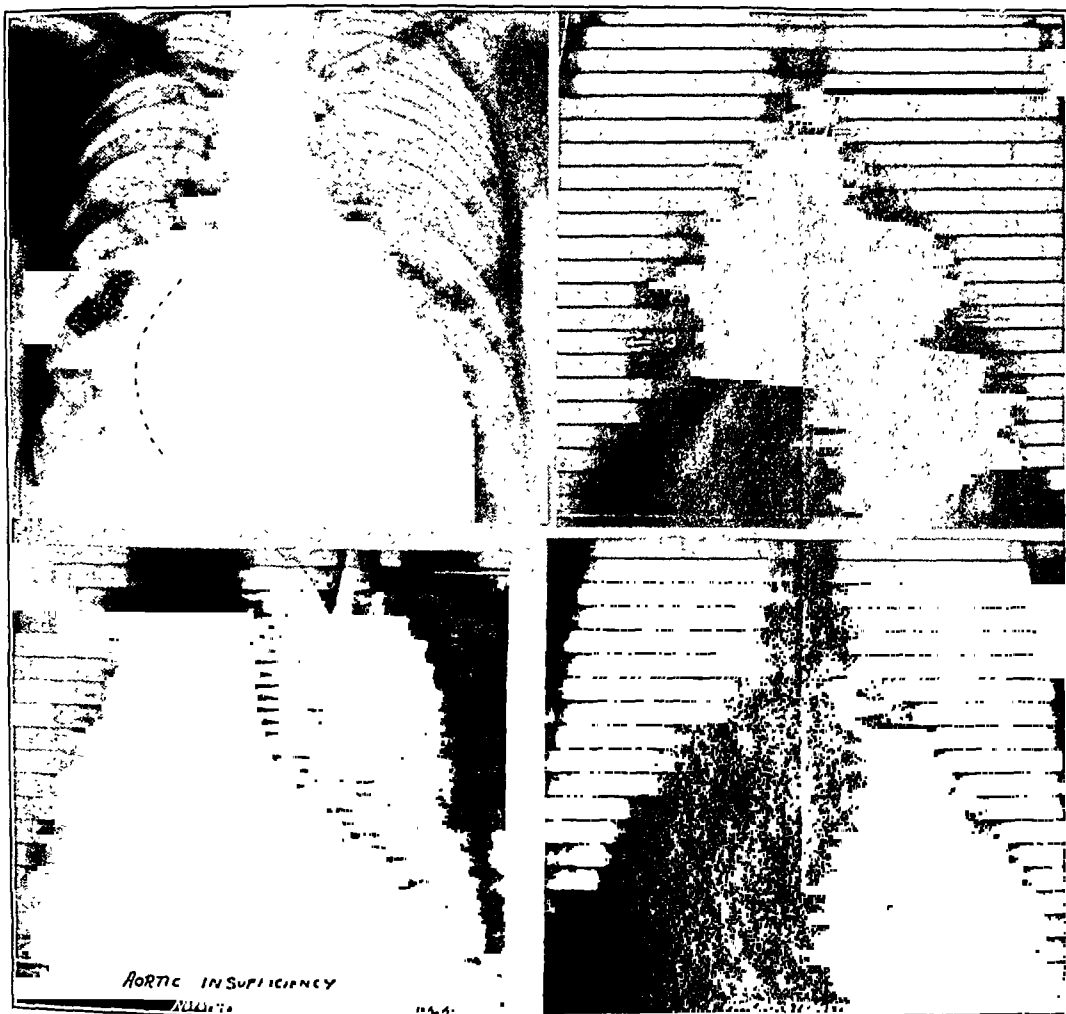


Fig.

Fig.

Fig. 11.—Mitral Insufficiency: *A*, The enlarged left auricle forms the right heart border. *B*, Roentgenkymogram shows regurgitation into the left auricle, with onset of systole and a rapid refilling of the left ventricle in early diastole.

Fig. 12.—Aortic Insufficiency. The aortic waves are of large amplitude and collapsing character. The ventricular waves are large, indicating an increased systolic ejection; and there is a rapid refilling in early diastole due to the regurgitation.

Fig. 13.—Aortic Stenosis. The aorta fills slowly during systole.

Aortic insufficiency produces striking changes in the kymogram (Fig. 12). The amplitude of the aortic wave is greatly increased, to a degree commensurate with the widened pulse pressure, and collapses early in diastole. The ventricular wave is likewise of large amplitude because of the increased ejection, and refills early in diastole as a result of the regurgitation.

In *aortic stenosis* the aorta fills very slowly because of the diminished rate of ejection from the ventricle. This change occurs only when there is a marked degree of stenosis (Fig. 13).

In general, kymography is not of great clinical value in valvular disease. There is considerable variation among normal subjects in the appearance of the ventricular waves, which may resemble those seen in mitral insufficiency or stenosis. Characteristic changes are generally produced only when the lesion is advanced. Furthermore, valvular lesions are usually multiple, and the kymographic waves are a resultant of the combined dynamic effect of these lesions. Thus, the aorta may fill slowly in cases of mitral insufficiency because of the diminished rate of ejection from the ventricle, since pressure is dissipated by regurgitation into the auricle; this may simulate the slow aortic filling in aortic stenosis.

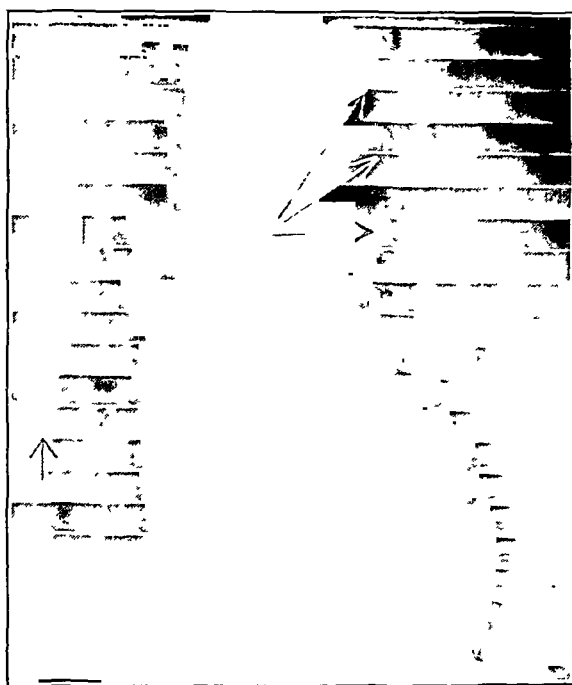


Fig. 14.—Aneurysm of the aorta.

DISEASES OF THE AORTA

Aneurysm.—It is frequently difficult to distinguish aortic aneurysms from mediastinal tumors, and kymography may help to identify the mediastinal mass. In general, aneurysms pulsate (Fig. 14), whereas solid tumors do not, but this statement requires many qualifications. Solid tumors situated in close proximity to the aorta may show transmitted movements which may be difficult to distinguish from the pulsations of the aorta. A helpful detail, when it is present, is the occurrence of cyclic density changes in aneurysm, in addition to movement at the border. An increased opacity of the mass which occurs at the same time as a lateral movement at the margin signifies movement in three dimensions, and indicates that the mass is expansile. Stumpff⁷ has devised a

densograph to aid in detecting variations in opacity. It is important to recognize that aneurysms may fail to pulsate if clotting has occurred in the sac. Fig. 15 illustrates a case of this type. A densely laminated aneurysm of the ascending aorta and innominate artery was found at autopsy. Scott and Moore¹⁵ have had similar experience. Blakemore and King¹⁸ demonstrated a marked reduction of pulsation following electrothermic coagulation of aortic aneurysms and found that "roentgenkymography has been of great help in showing the effect of induced clotting on the pulsation of aneurysm."

Syphilitic Aortitis.—The signs of aortitis are few, and any definite change in movement detectable in the kymogram would have definite clinical value. Unfortunately, syphilitic aortitis most often involves the ascending aorta, the first part of which is obscured by the heart shadow, and kymographic movements of the remainder of this segment of the aorta vary considerably because they are influenced by the motion of the heart, which is in close proximity. Scott, Moore, and McCordock¹⁹ stated that "the presence of large waves over the ascending aorta in adults below forty is most suggestive of syphilitic aortitis, and may be considered as such kymographically." In the posteroanterior view, the right side of the vascular shadow is formed by the superior vena cava, rather than the ascending aorta, in the majority of cases,⁸ unless the aorta is definitely widened. While it is true that bizarre waves, which may even resemble ventricular waves, may be seen over the right border of the vascular pedicle, these cannot be accepted as characteristic of syphilitic aortitis, for they are observed in normal individuals during expiration,²⁰ and in other pathologic conditions. It is also questionable whether they represent expansile movements of the aorta. The ascending aorta and aortic arch are best visualized in the slight left oblique position. In this view it is seen that there is considerable variation in the appearance of the wave of the ascending aorta in normal subjects. It will be necessary to establish normal standards in this position before any changes characteristic of aortitis can be distinguished.

Arteriosclerosis.—Arteriosclerosis decreases the elasticity of the aorta. The velocity of the pulse wave is a quantitative expression of arterial elasticity, the velocity increasing with decreased elasticity. An attempt has been made with the telekymogram to estimate pulse wave velocity, and thereby elasticity of the aorta, by employing Bramwell's formula relating change in arterial cross section to pulse pressure.¹⁰ With this method, normal values for pulse wave velocity in the descending aorta were estimated to be of a magnitude of 3 to 4 meters per second. Decreased arterial elasticity is frequently grossly distinguishable in the kymogram by the fact that the amplitude of the wave of the descending aorta is small although there are a normal or increased pulse pressure and a ventricular wave of normal magnitude. When calcific plaques are present in the aorta they may be seen to pulsate slightly.

The changes are usually more definite in the descending than in the ascending aorta, for arteriosclerosis more commonly involves the descending than the ascending portion. Furthermore, interpretation of movement of the ascending aorta is difficult because, in addition to its intrinsic expansile movement, there are probably an appreciable displacement of the ascending aorta by motion transmitted from the ventricles, and straightening of the aorta with increase in internal pressure (Bourdon action).

In hypertension the aortic wave may be of rather low amplitude. Since the aorta is already distended by a high diastolic pressure, its expansion in systole is consequently limited, and the kymographic wave of the descending aorta may appear rather small. The ventricular wave, however, is of normal or slightly increased amplitude, unless there is complicating myocardial damage.

DISEASES OF THE PULMONARY ARTERY

The waves of the pulmonary artery resemble those of the aorta closely; they are characterized by a rapid systolic outthrust succeeded by a gradual retraction, and the latter is interrupted by a prominent incisura. The diastolic collapse is somewhat more rapid than in the aorta. When the pulmonary artery shadow is increased in size as a result of disease the kymographic waves may vary, depending on the cause.

Patency of the ductus arteriosus (Fig. 16) causes waves of large amplitude in the pulmonary artery, reflecting an increased pulse pressure in the pulmonary circuit. This may be seen to extend to the larger branches in the hilar region. This phenomenon is known fluoroscopically as the "hilar dance."

With enlargement of the pulmonary conus secondary to mitral valvular disease the waves are of smaller amplitude than when the ductus arteriosus is patent, for the pulmonary artery is distended by a heightened diastolic pressure and its expansion is consequently limited (Fig. 17).

Aneurysm of the pulmonary artery is a rare lesion which is demonstrated well by kymography. Prominent arterial pulsations are present over the aneurysmal area (Fig. 18). In another case of pulmonary artery aneurysm recently observed by one of us, in which the diagnosis was confirmed at autopsy, there were also large pulsations. The small amplitude of the pulsations in the case of pulmonary artery aneurysm recently reported by Brown, McCarthy, and Fine²¹ may have been due to clotting within the sac.

ARRHYTHMIAS

Multiple-slit kymography is not well suited for the study of arrhythmias because of the short exposure usually employed. The type of grid devised by Cignolini⁶ permits a prolonged exposure and is better for this purpose, although at best roentgenkymography gives much less informa-

tion than electrocardiography with respect to the arrhythmias. The heart rate and time of onset and duration of systole and diastole may be accurately determined with the multiple-slit grid. Fig. 19 illustrates a case of heart block. The ventricular waves are of unusually large amplitude, indicating an increased systolic discharge resulting from the slow ventricular rate. Multiple, prominent, auricular waves are present over

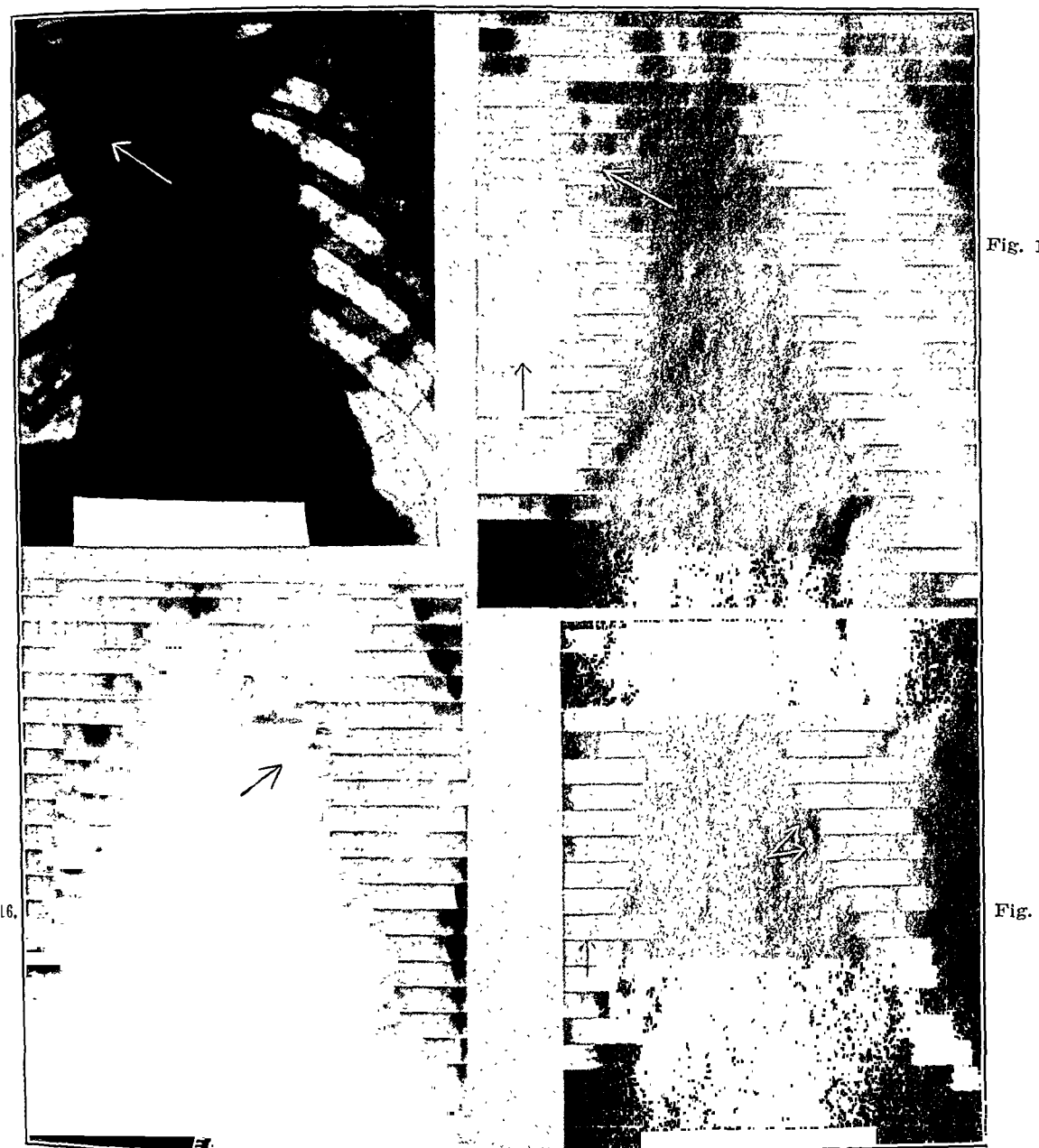


Fig. 15.—A, Aneurysm of the aorta and innominate artery. B, Roentgenkymogram shows no pulsations of the aneurysm. At autopsy the aneurysm was found to be densely laminated with mural thrombi.

Fig. 16.—Patent ductus arteriosus. The pulmonary artery pulsations are of increased amplitude.

Fig. 17.—Mitral valvular disease. The pulmonic conus is prominent but the pulsations are of lower amplitude than when the ductus arteriosus is patent.

the right heart border. Fig. 20 illustrates an extrasystole, which is of smaller amplitude than the regular beat.

Wolferth and Margolies²² demonstrated asynchronism in the onset of ejection from the two ventricles in bundle branch block by comparing the time of outthrust of the aortic and pulmonary arterial waves. Slight asynchronism between the two ventricles, of lesser degree, may occur normally.²³ A double peak in the ventricular wave has also been described in bundle branch block.²⁴ Some caution must be exercised in interpreting the ventricular waves in bundle branch block, since in these cases the heart is usually enlarged and the seat of considerable myocardial damage, which of itself may significantly alter the ventricular waves.

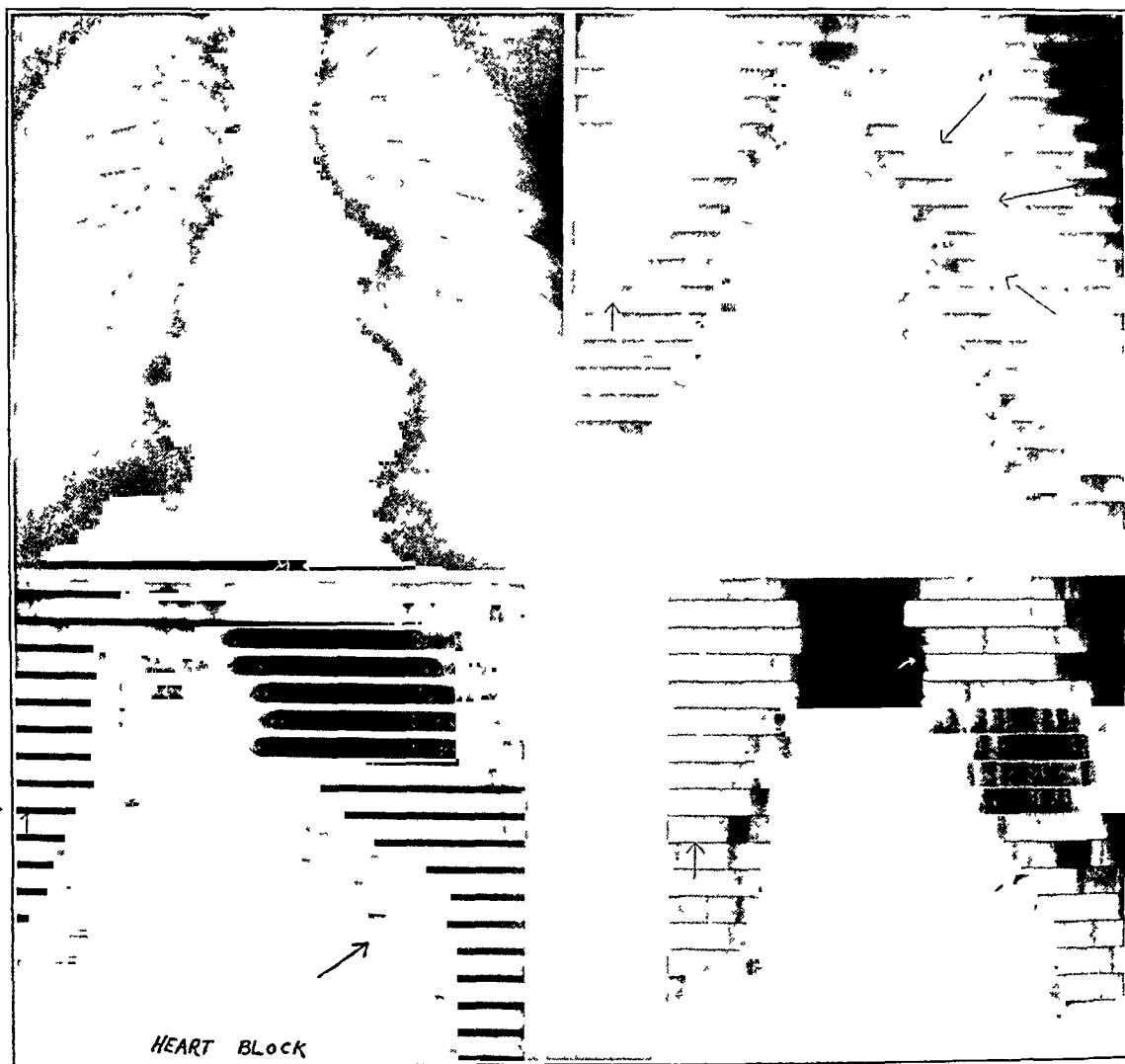


Fig. 18.—A, Aneurysm of pulmonary artery. B, Roentgenkymogram shows prominent pulsations.

Fig. 19.—Heart block. The ventricular wave is of large amplitude, indicating increased systolic ejection caused by the slow rate.

Fig. 20.—Extrasystole. The extrasystole is premature and of smaller amplitude than the preceding normal contraction.

SUMMARY

Roentgenkymography is a simple method of graphically recording the movements of the heart and great vessels, permitting an accurate and detailed analysis of the sequence of events throughout the cardiac cycle. The record is obtained on a single film with a short exposure of 1.5 seconds and entails no discomfort or hazard to the subject. The pulsations of the heart are recorded in the form of waves. The waves of the aorta and pulmonary artery correspond to arterial sphygmograms, while the ventricular waves resemble experimental ventricular volume curves.

In the interpretation of roentgenkymograms normal variations and certain important technical and physiologic factors must be considered before pathologic significance is attributed to changes which may be present.

The waves undergo changes of diagnostic significance in various pathologic states. The most important clinical application of kymography is in the detection of myocardial infarcts. Kymography may also be helpful in the diagnosis of constrictive pericarditis, pericardial effusion, and diseases of the pulmonary artery, and in distinguishing pulsating from nonpulsating tumors of the mediastinum. It is of little value in cases of valvular lesions except aortic insufficiency, in which characteristic changes occur.

While the method has limited clinical usefulness apart from these applications, there are other reasons why it is valuable. It provides a direct and convenient method for studying and teaching certain aspects of human cardiac physiology which have hitherto required difficult animal preparations employing the myocardiograph and arterial sphygmograph. In corroborating impressions of heart movement obtained by means of fluoroscopy it has given confidence to the radioscopist which is obtainable in no other fashion. It thus fills a definite need in the teaching field and should prove a most useful adjunct to fluoroscopic examination.

REFERENCES

1. Sabat, B.: Über ein Verfahren des röntgenographischen Darstellung der Bewegungen des Zwerchfells, des Herzens, der Aorta, *Lwowski Tygodnik Lekarski*, 6 Nr. 28 (July 13), 1911.
2. Stumpf, P.: Das röntgenographische Bewegungsbild und seine Anwendung (Flächenkymographie und Kymoskopie), Leipzig, 1931, G. Thieme.
3. Hirsch, I. S.: a. The Recording of Cardiac Movements and Sounds by the Roentgen Ray, *Radiology* 22: 403, 1934.
b. The Examination of the Heart by the Roentgenkymographic Method, *Brit. J. Radiol.* 7: 728, 1934.
4. Johnson, S. E.: Kymograph as New Aid in Diagnosis of Adhesive Pericarditis, *Surg., Gynec. and Obst.* 61: 169, 1935.
5. Scott, W. G., and Moore, S.: The Construction of Roentgenkymographs and Kymoscopes, *Radiology* 26: 622, 1936.
6. Cignolini, P.: Die Röntgenkymographie mit unterbrochenem Schlitz, *Fortschr. a. d. Geb. d. Röntgenstrahlen* 49: 224, 1934.
7. Stumpf, P.: Die objektive, laufende Messung der Schattentiefe von Röntgenbildern und ihre Bedeutung für die Diagnostik (Densographie), *Fortschr. a. d. Geb. d. Röntgenstrahlen* 36: 695, 1927.

8. Hirsch, I. S., and Gubner, R.: Application of Roentgenkymography to the Study of Normal and Abnormal Cardiac Physiology, *AM. HEART J.* 12: 413, 1936.
9. Johnson, S. E.: Roentgen Kymography Considered in Relation to Heart Output, and a New Heart Index, *Am. J. Roentgenol.* 37: 167, 1937.
10. Ungerleider, H. E., and Gubner, R.: Teleroentgenkymography; Its Application to the Study of Heart Size, Output, and Aortic Elasticity, *Radiology* 33: 497, 1939.
11. Schilling, C.: Die Anwendung der Flächenkymographie in der Diagnostik der Herzkrankungen, *Fortschr. a. d. Geb. d. Röntgenstrahlen* 47: 241, 1933.
12. Stumpf, P.: Die Erscheinungsformen der Herzmuskelerkrankungen in Flächenkymogram, *Fortbildungs-Lehrgang in Bad-Nauheim* 10: 67, 1934.
13. Gubner, R., and Crawford, J. H.: Roentgenkymographic Studies in Myocardial Infarction, *AM. HEART J.* 18: 8, 1939, and *J. Clin. Investigation* 17: 507, 1938.
14. Tennant, R., and Wiggers, C. J.: The Effect of Coronary Occlusion on Myocardial Contraction, *Am. J. Physiol.* 112: 351, 1935.
15. Scott, W. G., and Moore, S.: Roentgenkymographic Studies of Aneurysms and Mediastinal Tumors, *Am. J. Roentgenol.* 40: 165, 1938.
16. Kirch, E.: Pathogenese und Folgen der Dilatation und der Hypertrophie des Herzens, *Klin. Wehnschr.* 9: 769, 1930, 9: 817, 1930.
17. Esser, C.: Über das kymographische Verhalten der Herzspitze bei ausgesprochener Dilatation, *Fortschr. a. d. Geb. d. Röntgenstrahlen* 52: 213, 1935.
18. Blakemore, A. H., and King, B. G.: Electrothermic Coagulation of Aortic Aneurysms, *J. A. M. A.* 111: 1821, 1938.
19. Scott, W. G., Moore, S., and McCordock, H. A.: Roentgen Kymographic Studies of Cardiac Conditions, *Radiology* 28: 196, 1937.
20. Weltz, G. A.: Die Atmungsbewegungen des Herzens und der grossen Gefässe, *Verhandl. d. Gesellsch. f. Kreislaufforschung* 8: 98, 1935.
21. Brown, S., McCarthy, J. E., and Fine, A.: The Pulmonary Artery—A Roentgenographic and Roentgenkymographic Study, *Radiology* 32: 175, 1939.
22. Wolferth, C. C., and Margolies, A.: Asynchronism in Contraction of the Ventricles in the So Called Common Type of Bundle Branch Block, *AM. HEART J.* 10: 425, 1935.
23. Katz, L. N.: Asynchronism of Right and Left Ventricular Contractions and Independent Variations in Their Duration, *Am. J. Physiology* 72: 655, 1925.
24. Heckmann, K.: Explanation of Double Peaks of Marginal Waves in Surface Cardiokymogram, *Klin. Wehnschr.* 15: 644, 1936.

ADDITIONAL BIBLIOGRAPHY

- Stumpf, P., Weber, H. H., and Weltz, G. A.: Röntgenkymographische Bewegungslehre innerer Organe, Leipzig, 1936, G. Thieme.
- Bordet, E., and Fischgold, H.: Radiokymographie du coeur et des vaisseaux, Paris, 1937, Masson et Cie.
- Ludwig, H.: Negatives und Positives von der Herzkymographie, *Fortschr. a. d. Geb. d. Röntgenstrahlen* 54: 469, 1936.
- Westermarck, N.: Studien über die Bewegungen des Herzens, *Acta Radiol.* 17: 235, 1936.
- Cottenot, P., and Heim de Balsac, R.: Étude de Kymographie Cardio-Vasculaire, *Ann. de Med.* 39: 24, 1936.
- Klioner, I., and Ivanov, N.: Die normale Herzkurve und die physiologischen Veränderungen derselben im Flächenkymogram, *Fortschr. a. d. Geb. d. Röntgenstrahlen* 51: 469, 1935.
- Zdansky, E., and Ellinger, E.: Röntgenkymographische Untersuchung am Herzen, *Fortschr. a. d. Geb. d. Röntgenstrahlen* 47: 648, 1933.
- Fetzer, H.: Die Anwendung der Röntgenkymographie in der Kreislaufdiagnostik, *Ergebn. d. inn. Med. u. Kinderh.* 45: 485, 1933.
- Zierach, H. J.: Untersuchungen über die Konstanz der röntgenographisch darstellbaren Bewegungen des Herzens, *Fortschr. a. d. Geb. d. Röntgenstrahlen* 50: 16, 1934.
- Ihre, B.: Röntgenkymography ad Modum Stumpf as Method of Examining the Heart, *Acta Radiol.* 15: 107, 1934.

CORONARY EMBOLISM

REPORT OF THREE CASES

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CORONARY embolism was described by Virchow¹ as early as 1856, but an exhaustive review of the literature, made by Saphir² in 1933, indicates that it is not a common condition, for he was able to find only eleven cases in which the diagnosis was satisfactorily proved. To these he added three of his own. The rarity of this disease has been variously attributed to the difference between the caliber of the aorta and that of the coronary arteries;³ the situation of the coronary vessels at the root of the aorta; the right angle of emergence of the coronary arteries; the bulk and swiftness of the blood current in this portion of the aorta;⁴ and the fact that the major part of coronary filling occurs in diastole.²

The emboli are usually detached portions of endocardial vegetations, fragments of arteriosclerotic plaques, or bits of disrupted mural thrombi, but they may consist of air, fat, tumor tissue, or inflammatory tissue. The left coronary artery, and especially its descending ramus, is the vessel which is most commonly obstructed. As death frequently ensues shortly after the occlusion, associated myocardial changes are not often found when the autopsy is performed. Because it is not always possible to identify an embolus by gross or microscopic examination of the occluded vessel, it is important to demonstrate a possible source for the embolus. Furthermore, the obstructed artery must be free from other disease which would be sufficient in itself to cause the occlusion. If these two criteria are fulfilled, the diagnosis can be established with reasonable certainty even in those cases in which the embolus has the structure of an ordinary thrombus.

The clinical diagnosis of coronary embolism is difficult because death is usually dramatically sudden. In those rare instances in which the course is more gradual, the possibility should be considered if there is evidence of coronary occlusion in the absence of coronary artery disease, and if a possible source for an embolus can be demonstrated.

In the past twenty years there have been three instances of coronary embolism among 12,300 consecutive autopsies performed at Cleveland City Hospital. These cases are of particular interest, in that death was more or less gradual, and myocardial infarction had developed in two instances.

CASE 1.—J. B., a white man, 42 years of age, who entered Cleveland City Hospital June 14, 1938, complained of chills and fever. He had been in good health until one month previously, since which time he had had malaise, anorexia, weakness, diaphoresis, and daily chills and fever. There was no history of rheumatic fever.

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Received for publication June 27, 1939.

Examination showed that the patient was normally developed, but emaciated and seriously ill. The temperature was 39.2° C., and the pulse rate was 100 beats per minute. There were several petechiae over the trunk. The lungs were normal. Auscultation of the heart revealed a loud, blowing, systolic murmur, heard best at the apex. The blood pressure was 108/60.

The erythrocytes numbered 3,620,000 per cubic millimeter, and the hemoglobin was 55 per cent. The leucocyte count was normal. The urine was normal, and the blood Kline test for syphilis was negative. Fluoroscopic and roentgenographic studies of the chest showed that the heart was of normal size and shape.

During the patient's stay in the hospital the temperature varied between 36.7° C. and 40.5° C. On numerous occasions petechiae were present in the retinae and the skin. Nevertheless, twenty-three blood cultures were negative. Albumin, casts, leucocytes, and erythrocytes appeared in the urine. The hemoglobin fell to 38 per cent. Serial roentgenograms of the chest showed progressive enlargement of the heart; the transverse diameter increased from 13.2 cm. to 16.5 cm. The greatest internal diameter of the chest was 34 cm. At no time did the patient complain of pain in the chest. An electrocardiogram taken July 18 showed no abnormalities. He died August 17, on the one hundredth day after the onset of his illness. The clinical diagnosis was subacute bacterial endocarditis and acute focal glomerulonephritis.

Autopsy Findings.—(Autopsy No. A-12294, performed by Dr. T. C. Laipply, four hours after death.) The body was that of a normally developed but poorly nourished white man, approximately 47 years old. There was marked pallor of the skin and mucous membranes, and numerous petechiae and large ecchymoses were present in the skin and conjunctivae. The pericardial sac contained 25 c.c. of cloudy, amber fluid, and the lining surface was dull, gray, and covered by flecks of fibrin.

The heart weighed 450 gm. All of the chambers were dilated. The wall of the right ventricle measured 4 mm. in thickness, and that of the left, 18 mm. The epicardium was covered by a dull, granular exudate. There was a fusiform bulge in the descending ramus of the left coronary artery. This measured 7.5 mm. in diameter, and was situated 7.5 cm. distal to the left coronary ostium. There was a similar, smaller bulge in the terminal branch of the left circumflex ramus, and another in the terminal branch of the right coronary artery. The exudate over these bulges was thicker than elsewhere, and small hemorrhages could be seen in the surrounding subepicardial fat. Sections through these bulges showed that in each instance the artery was plugged with soft, friable, mottled, yellowish-gray and pale-brown debris which was loosely attached to the intima. Proximal and distal to the occlusions the vessels contained only post-mortem blood clots and showed no arteriosclerosis. Involving the apex of the left ventricle and the interventricular septum there was a well-circumscribed infarct which measured 6 cm. across. In this area the ventricular wall was thinner than elsewhere, and the muscle was mottled yellowish-brown and dusky gray. The endocardium lining all chambers was normal except in the region of the infarct, where it was thickened and opaque. The anterior mitral leaflet was severely deformed by bulky, grayish-brown vegetations which were firmly attached to its margin, and the central portion of the leaflet was ulcerated. The vegetations extended downward on the chordae tendineae to the tips of the papillary muscles, and a few of the chordae were ruptured. The posterior mitral leaflet was thickened at the right commissure, but was otherwise normal. The remaining valves showed no evidence of endocarditis.

The aorta was of normal thickness and elasticity. There were edema of the lungs, cloudy swelling of the parenchymatous organs, and acute hyperplasia of

the spleen. There were infarcts of the spleen and both kidneys. The kidneys were large, swollen, and pale pinkish-yellow. Their surfaces were dotted with tiny hemorrhages, and the striations as seen on the cut surfaces were indistinct. There were small petechiae in the mucosa of the renal pelves, the urinary bladder, and the gastrointestinal tract. A few were seen in the pia-arachnoid over the frontal and parietal lobes.

Microscopic examination of a section of the affected portion of the anterior mitral leaflet showed that the vegetations had the characteristics of those of endocarditis lenta. They were composed of undulating layers of fibrin, necrotic debris, and bacteria which stained poorly. There were small areas of ulceration, tiny thrombi attached to the surface, and a gradual transition through granulation tissue into the substance of the valve leaflet. There was nothing to establish the existence of rheumatic endocarditis. Sections through the occluded arteries showed that they were distended with plugs of fibrin, debris, and bacteria identical with those in the vegetations. The lumina were greatly enlarged. The walls were thin, as if stretched, and were the seat of severe, acute, exudative arteritis. The surrounding fat was densely infiltrated by polymorphonuclear leucocytes, and the epicardium was covered by a thick layer of acute inflammatory exudate. Proximal and distal to the occlusions the coronary arteries were normal. The changes in the myocardium were those characteristic of a septic infarct.

The kidneys were the seat of acute focal glomerulonephritis. *Streptococcus viridans* was recovered from the heart's blood and from the vegetations on the mitral valve.

The diagnosis was subacute bacterial endocarditis of the mitral valve, with discharge of emboli, occlusion of the left descending and terminal branches of the left circumflex ramus and right coronary artery, and infarction of the apex of the left ventricle.

CASE 2.—F. Z., a white man, 44 years of age, who entered Cleveland City Hospital Oct. 3, 1931, complained of fever and chills. The patient had been in excellent health until one month earlier, when he had begun to have malaise, weakness, anorexia, nausea, vomiting, severe generalized abdominal pain, lumbar backache, fever, and chills. Two days thereafter his legs started to swell and he became short of breath. After two weeks the abdominal and back pain decreased in severity, but the other symptoms became worse. There was no thoracic pain at any time.

Examination showed that the patient was well developed and well nourished, but acutely ill. The temperature was 40° C., the pulse rate was 120 per minute, and the respiratory rate was 40 per minute. There were numerous petechiae in both conjunctivae. There were râles in the bases of both lungs. The cardiac activity and sounds were feeble. A protodiastolic gallop rhythm was present, and there was a question whether or not a pericardial friction could be heard. The cardiac mechanism was normal, and the blood pressure was 100/60. The abdomen was distended, and there was fullness in the region of the liver. The legs and sacral region were edematous.

The erythrocyte count, hemoglobin value, and blood urea nitrogen level were normal. The blood Kline test for syphilis was negative. The leucocytes numbered 11,000 per cubic millimeter. The urine contained albumin (grade 3) and leucocytes (grade 1). The blood culture yielded a *Staphylococcus albus* on two occasions. The electrocardiogram in the conventional leads showed an elevation of the ST segment in Lead I and depression of the ST segment in Leads II and III.

The patient became progressively worse and died on the second hospital day. The clinical diagnosis was recent coronary thrombosis with myocardial infarction, myocardial insufficiency, septicemia due to *Staphylococcus albus*, and bronchopneumonia.

Autopsy Findings.—(Autopsy No. 7764, performed by Dr. C. J. Farinacci, four hours after death.) The body was that of a well-developed, obese, white man, approximately 45 years old. There were numerous petechiae in both conjunctivae, but none was seen in the skin. The heart weighed 475 gm. and was moderately dilated. Except for a dull, granular, dark-red patch, 3 cm. in diameter, near the apex of the left ventricle, the epicardium was smooth and transparent. The myocardium was of normal color except in the anterior, apical portion of the left ventricle, where there was a recent infarct. The affected muscle was dark-red and softer than normal. The endocardium lining all chambers was smooth. The mitral leaflets were thickened and fibrotic, particularly along their free margins. The aortic leaflets were also thickened, and nodular vegetations varying in diameter from 1.5 to 5 mm. were attached to the margin of each. The tricuspid and pulmonic valves were normal. There were a few atheromatous plaques on the intima of the coronary arteries, but their walls were not significantly thickened. The lumen of the terminal branch of the left descending ramus was occluded by an embolus lodged just proximal to the infarct.

The aorta was normal except for slight arteriosclerosis about the ostia of the intercostal arteries. There was passive hyperemia of the lungs and abdominal viscera. The spleen was the seat of acute hyperplasia, and recent infarcts were present in the spleen and both kidneys. Small hemorrhages stippled the mucosa of the renal pelves, the urinary bladder, and the gastrointestinal tract. The brain and spinal cord were normal.

Microscopically, the lesion in the myocardium had all of the features of a septic infarct; there were many clumps of cocci in pairs and packets between the necrotic muscle fibers and in the capillaries. The coronary arteries beyond the occlusion showed small patches of intimal thickening and hyalinization, but in none of the sections examined had this disease significantly reduced the caliber of the lumen. The infarcts in the spleen and kidneys also contained clumps of bacteria.

This was a case of acute endocarditis superimposed upon an old rheumatic endocarditis of the aortic valve, with an embolus plugging the terminal branch of the descending ramus of the left coronary artery and a septic infarct of the anterior, apical portion of the left ventricle.

CASE 3.—C. L., a white man twenty-six years of age, who entered Cleveland City Hospital Dec. 21, 1918, complained of "heart trouble." The patient was known to have had rheumatic heart disease since an attack of rheumatic fever at the age of 19. During the three months previous to admission he had had malaise, weakness, anorexia, night sweats, and fever, and had lost 45 pounds in weight.

Examination showed that the patient was normally developed, but poorly nourished and acutely ill. The temperature was 38° C., and the pulse rate was 114 per minute. The eyegrounds and conjunctivae were normal. The heart was enlarged both to the right and left. There were systolic and diastolic murmurs at the apex and at the aortic area. The cardiac mechanism was normal, and the blood pressure was 148/78. The lungs were normal. The edge of the liver was 3 cm. below the costal margin; the spleen was enlarged to percussion but could not be palpated.

Roentgenologic examination of the chest showed that the heart was enlarged in all dimensions. The erythrocytes numbered 2,500,000 per cubic millimeter, and the value of the hemoglobin was 50 per cent. Urinalysis was negative except for albumin (1 plus). Numerous blood cultures failed to show any growth.

The patient became progressively worse. The fever was intermittent, the temperature varying from 36° C. to 39.5° C. On March 2 he complained of sudden, severe pain in the lower part of the left leg. The dorsalis pedis artery was found to be pulseless, and in the next two weeks the left foot and toes showed ischemic necrosis.

At 8:00 A.M. on April 27 the patient suffered severe upper thoracic pain which radiated to the epigastrium and was relieved only by morphine. The following day, at 2:30 P.M., he died suddenly.

The clinical diagnosis was rheumatic heart disease with mitral stenosis and insufficiency and aortic insufficiency, cardiac hypertrophy and dilatation, bacterial endocarditis, and embolism of the left dorsalis pedis artery with ischemic necrosis of the toes of the left foot.

Autopsy Findings.—(Autopsy No. 1106, performed by Dr. Maurice L. Richardson.) The body was that of a poorly nourished white man. There was ischemic necrosis of the left foot and the great toe was mummified.

The heart weighed 630 gm. and was dilated, particularly on the right side. The epicardium was normal. The myocardium was pale and showed diffuse fibrosis, but there were no infarcts. The mitral valve was severely deformed, and the orifice measured only 2.5 cm. in diameter. Both leaflets were greatly thickened and the chordae tendineae were robust and rigid. There were bulky, gray vegetations on the free margins, with ulceration of both leaflets. The aortic leaflets were thickened, deformed, and fused at the left posterior commissure. There were vegetations and ulcers on the posterior and left anterior leaflets, and the process had extended into the aorta to a point 5 mm. above the aortic sinuses. The tricuspid and pulmonic valves were anatomically normal. At the bifurcation of the left coronary artery there was an embolus which completely occluded the descending ramus.

The thoracic and abdominal segments of the aorta were normal. The left posterior tibial artery was partially filled with a soft necrotic mass. Its wall was ulcerated and had perforated at one point to give rise to a large hematoma between the calf muscles. There was severe chronic passive hyperemia of the lungs and liver. The spleen was the seat of acute hyperplasia, and the spleen and left kidney contained septic infarcts.

Microscopic sections revealed small collections of polymorphonuclear leucocytes scattered throughout the myocardium. These were usually situated in the supporting connective tissue, frequently near small blood vessels. The muscle fibers were large, and many of the nuclei had square poles. There was considerable fragmentation, but the striations were preserved. The infarcts of the spleen and left kidney were typical, and random sections of the kidneys showed acute focal glomerulonephritis.

The diagnosis was chronic rheumatic heart disease, superimposed subacute endocarditis of mitral and aortic valves with extension of the vegetations upward about the ostia of the coronary arteries, and embolism of the left coronary artery with occlusion of the descending ramus.

COMMENT

Clinically, the first case was typical of subacute bacterial endocarditis except that numerous blood cultures were negative. There was nothing during life to suggest myocardial infarction or coronary embolism. The absence of pain would suggest that the infarction was painless or that the patient's sensibility was so blunted that he did not appreciate pain. The electrocardiogram was normal but had been taken one month before death. Post-mortem examination, however, established the fact that coronary embolism was present. There were ulcerated vegetations on the mitral valve, and the embolus was histologically indistinguishable from these vegetations. The wall of the

coronary artery showed only such changes as were secondary to the embolus, and the resulting infarct was septic. The case was unusual in that death was not sudden, and infarction had occurred. The presence of three distinct emboli was also noteworthy.

In the second case, clinically, there was evidence of infarction and septicemia; the two processes, however, were not thought to be related. Post-mortem examination established the diagnosis in this case, also; the vegetative endocarditis of the aortic valve was an obvious source for the embolus, the wall of the occluded vessel was normal, and there was a septic infarct in the myocardium.

In the third case, the sudden death of a patient known to have rheumatic heart disease, bacterial endocarditis, and embolic occlusion of an artery of an extremity might well have been thought to be due to coronary embolism, but sudden death in cases of heart disease can result from other causes, so that even in retrospect a clinical diagnosis of embolism would not seem justified. The ulcerative endocarditis of either the mitral or aortic valves was the source of the embolus, and no other cause for occlusion of the coronary artery was demonstrable.

SUMMARY

Three cases of coronary embolism were encountered among 12,300 consecutive autopsies at Cleveland City Hospital. In none was the diagnosis made clinically. The source of the emboli in each instance was an ulcerative endocarditis of either the aortic or mitral valves. Myocardial infarction occurred in two cases.

ADDENDUM

Since this paper was submitted for publication, one of the authors (J. L. W.) has examined another case of coronary embolism at the St. Alexis Hospital of Cleveland, Ohio. The patient, a white man, 45 years of age, who was considered to have subacute bacterial endocarditis because a blood culture had yielded a growth of *Streptococcus viridans*, died suddenly while being moved in a wheel chair. The autopsy revealed hypertrophy and dilatation of the heart and subacute bacterial endocarditis of the aortic valve. Two emboli, composed of material identical with that on the heart valves, were present in branches of the descending and circumflex rami of the left coronary artery. The branch of the descending ramus was occluded at its origin, and the circumflex ramus at its bend into the posterior longitudinal sulcus. Proximal and distal to the occlusions both arteries were normal. There was no infarction of the myocardium.

REFERENCES

1. Virchow, R.: Ueber capilläre Embolie, Virchows Arch. f. path. Anat. 9: 307, 1856. The same case, with more details, is given in *Gesammelte Abhandlungen zur wissenschaftlichen Medicin*, p. 711, Frankfurt, 1856, Meidinger and Co.
2. Saphir, O.: Coronary Embolism, AM. HEART J. 8: 312, 1933.
3. Marie, R.: L'Infarctus du Myocarde, Thèse pour le Doctorat en Médecine, Carré, G., and Naud, C., Paris, 1896.
4. Powell, R. D.: Diseases of the Myocardium, in Allbutt and Rolleston's "A System of Medicine by Many Writers" 6: 105, London, 1909, The Macmillan Co.

Department of Clinical Reports

BACTERIAL ENDOCARDITIS DUE TO THE STREPTOCOCCUS FECALIS

REPORT OF A CASE

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THE *Streptococcus viridans* is commonly mentioned as the causative organism in cases of subacute bacterial endocarditis (recurrent endocarditis, endocarditis lenta), with occasional reference to the gonococcus, influenza bacillus, and others, as organisms capable of producing the disease in rare instances. Careful search of the Index Medicus and Catalogue of the Army Medical Library revealed several reports of cases of enterococcal endocarditis, but none in which the *Streptococcus fecalis* was named as the causative agent. Since the enterococci comprise a large group, of which *Streptococcus fecalis* is a member,¹ it is possible that several of the reported cases were caused by the latter organism. With one exception,² the reports appeared in foreign journals. The purpose of this paper is to present a case on the borderline between acute and subacute bacterial endocarditis, in which careful bacteriologic studies identified the causative organism as *Streptococcus fecalis*.

Streptococcus fecalis was first described by Andrewes and Horder, in 1906,³ and its classification worked out on the basis of earlier investigations by Gordon (1903-4). Andrewes and Horder found the organism in the blood before and after death in four out of twenty-four cases of "malignant" endocarditis. They considered it an organism of rather feeble pathogenicity, closely related to *Streptococcus salivarius* (a species of the viridans group), one passing into the other "by insensible gradations." This conception of a very close relationship has been held by many later writers. It is hardly necessary to mention the difficulties involved in classifying the streptococci, nor will space permit a discussion of this problem. However, recent work by Sherman⁴ makes possible a more decisive separation of *Streptococcus fecalis* from members of the viridans group.

Streptococcus fecalis belongs to the large group of streptococci known as the enterococci, which are characterized by heat resistance, bile tolerance, and the ability to ferment manitol. Sherman⁵ points out the inadvisability of classifying streptococci by their action on blood alone. He considers as hemolytic only those organisms which produce a clear-

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The bacteriologic studies were carried out by Drs. W. D. Eaton and W. G. Stewart. Received for publication May 27, 1939.

cut beta hemolysis; all others, which produce the lesser degrees of hemolysis designated as alpha and gamma, are considered nonhemolytic. Thus both *Streptococcus viridans* (alpha hemolysis) and *Streptococcus fecalis* (gamma hemolysis) fall into the "nonhemolytic" group, and Sherman has stated that "the question of how frequently strains of *Streptococcus viridans* isolated from cases of endocarditis are in fact organisms of another group is as yet unanswered." Recently, further evidence, based on serologic reactions, justifying the division of the enterococci from the viridans group has been offered by Sherman,⁴ who sought to extend the unpublished observations of Lancefield (1937). She had found that cultures of *Streptococcus fecalis* and *Streptococcus liquefaciens*, both members of the enterococcus group, belonged serologically to the Lancefield Group D. Sherman worked with more than fifty cultures of *Streptococcus fecalis*, identified by physiologic studies. The strains were taken from human feces, milk, ice cream, and cheese, and they included organisms from the blood in this case, sent by Dr. E. G. D. Murray. In each instance, the strains were found to belong to Lancefield Group D. Furthermore, similar work done on *Str. liquefaciens* and *Str. durens*, both recognized members of the enterococcus group, placed those organisms in Lancefield Group D. *Str. zymogenes*, a fourth recognized species of enterococcus, was first used to establish Lancefield Group D. Members of the viridans group (*Str. salivarius*, *Str. equinus*, etc.) are serologically heterogeneous.

REPORT OF CASE

History.—Mrs. B. L., a French Canadian, aged 30, was admitted to the service of Dr. C. F. Moffat, Royal Victoria Hospital, Nov. 15, 1937. She had had attacks of fever with polyarthritides, diagnosed as rheumatic fever, which began at the age of three and recurred every winter for ten years. At the age of seven, she had severe choreiform movements and extreme nervousness, necessitating her admission to a hospital. At the age of 25 she had another attack of polyarthritides and fever. Three years later, at the age of 28, she became pregnant and began to show signs of cardiac decompensation. She was dyspneic and orthopneic and was forced to spend a long period in bed following delivery. She then enjoyed fairly good health until August, 1937, two years later, at which time she had a spontaneous abortion in the second month of pregnancy. In the same month, two feet of segmented flatworm were passed after the administration of an anthelmintic. In the middle of September, 1937, she had an attack of acute polyarthritides involving the left extremities, associated with weakness, anorexia, and nausea with occasional vomiting. After two weeks of rest in bed the polyarthritides disappeared, but during the succeeding two weeks the number of her bowel movements increased to three or four a day, defecation was accompanied by tenesmus, and the stools were watery and green. At the same time she began to notice rather severe pain in both upper quadrants of the abdomen. This state of affairs continued until the day of her admission to the hospital, Nov. 15, 1937, two months after the onset of the attack of acute polyarthritides. She observed a tender, slightly reddened elevation on the medial surface of her right thumb one week prior to admission, and a change in the appearance of her urine, which became the color of porter four days before admission. There had been a weight loss of 15 pounds in the two preceding months.

Two brothers and one sister had had rheumatic fever. The past history and functional inquiry revealed nothing of additional significance.

Physical Examination.—The temperature was 98°F., the pulse rate 120, and the respiratory rate 45. The patient was an emaciated and pale young woman, markedly dyspneic. The skin had the so-called café-au-lait appearance, but this was said to be her usual color. There was slight clubbing of the fingers, but no peripheral edema. The teeth were carious, and there was a marked gingivitis. Examination of the cardiovascular system revealed a rapid, regular pulse of poor volume; pulsation of the neck veins; an apical diastolic thrill; enlargement of the heart to percussion; a loud, booming first sound with a mitral presystolic murmur at the apex; a soft, blowing diastolic murmur at the pulmonic area; and softening of the aortic second sound, with a suggestion of a diastolic murmur. The blood pressure was 108/52. The chest expanded normally on both sides. There were fine crepitations at the left base posteriorly, but the lungs were otherwise normal to percussion and auscultation. There was generalized tenderness over the abdomen, and the liver and spleen were palpable below the costal margin, the former for a distance of four, the latter for a distance of three, fingerbreadths. Examination of the locomotor and nervous systems contributed nothing of (diagnostic) significance. No petechiae were seen at any time. The clinical impression formed from the above findings was that she had rheumatic heart disease of long standing, with a moderate degree of decompensation, mitral stenosis and insufficiency, aortic insufficiency, and subacute bacterial endocarditis.

Laboratory and Special Examinations.—The urine was acid in reaction, had a specific gravity of 1.020, and contained albumin (4 plus), acetone (2 plus), 6 to 10 leucocytes per high-power field, and great numbers of erythrocytes. The hemoglobin was 58 per cent (9 gm.), the erythrocyte count 3,400,000 and the leucocyte count 12,600. The uric acid content of the blood was 4.84 mg. per cent, the nonprotein nitrogen, 44 mg. per cent, the total protein nitrogen, 940 mg. per cent, and the sugar, 159 mg. per cent. The electrocardiogram showed normal rhythm, normal A-V conduction time, low voltage of the QRS complexes, and depression of the S-T intervals in Leads I and II. A blood culture taken on the day of admission yielded a pure culture of organisms which were at first placed tentatively in the enterococcus group because of their heat resistance. Further physiologic studies identified the organism as *Streptococcus fecalis*. A strain was sent to Dr. J. M. Sherman, who confirmed the classification and carried out the studies mentioned above, in which this organism, along with others of the same species, was found to belong to Lancefield Group D. Another blood culture, taken a few days later, gave identical results.

Progress.—The patient grew steadily worse, and died November 25, ten days after admission and approximately ten weeks after the onset of the final episode. The temperature fluctuated between 101 and 104° F., with progressive pallor, weakness, and prostration, and increasing splenomegaly, abdominal tenderness, and distention.

Autopsy.—The heart was not enlarged (300 gm.). Focal fibrous pericardial adhesions were seen between the pulmonary artery and right auricular appendage. The left ventricular myocardium was dark red, soft, and its wall measured only 1 cm. in thickness. The mitral valve showed diffuse thickening of the cusps and slight narrowing of the orifice (8 cm.), with projecting, friable, pale gray polypoid vegetations along the free edge, almost filling the valve opening. The anterior and left posterior cusps of the aortic valve were thickened and fused, presenting at the point of fusion many smaller, but similar, vegetations.

Microscopic Examination.—Sections from the left ventricular wall showed a focal productive myocarditis, with occasional nodules of large, pale cells lying in perivascular tissue. No Aschoff bodies were seen. Sections from the left auricle

showed marked fibrous thickening of the endocardium and some hypertrophy of the muscle. Examination of the polypoid vegetations and the underlying valvular tissue revealed marked, hyaline, fibrous-tissue thickening of the valve, surmounted by a large mass composed of laminated fibrin containing many disintegrating leucocytes, and a zone of granulation tissue. There was a marginal mass of fibrin containing many cocci arranged in short chains and pairs, staining a deep blue with Gram's stain. There were several other interesting autopsy observations. The spleen was only slightly enlarged (155 gm.), and showed an extremely soft, necrotic middle third, with the capsule everywhere intact. The microscopic appearance was typical of infarction.

The peritoneal cavity contained 100 c.c. of thick, purulent material, and the parietal peritoneum over the left lateral and posterior surfaces showed a diffuse reddening which involved loops of bowel, as well. The spleen was attached to the diaphragm above, and to the transverse colon below, by fragile, fibrinous adhesions. These findings pointed to a direct relationship between the large splenic infarct and the peritonitis.

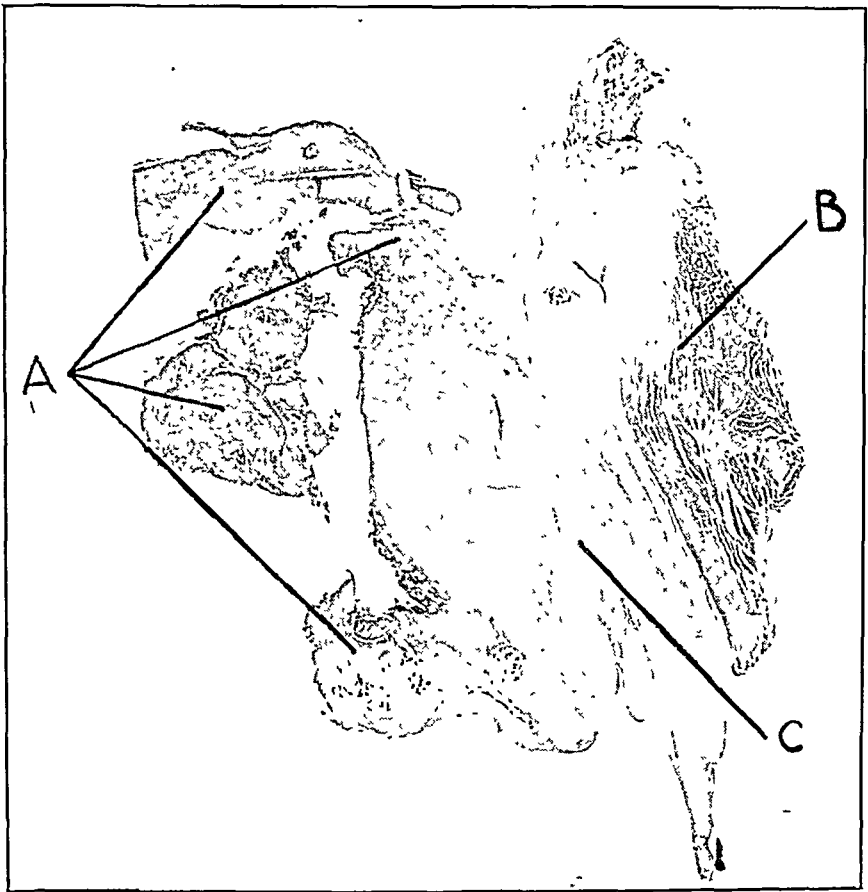


Fig. 1.—Low-power view of mitral valve with recent vegetation. *A*, recent vegetation (fragmented); *B*, wall of left ventricle; *C*, greatly thickened mitral valve (old productive endocarditis).

Each pleural cavity contained approximately 250 c.c. of slightly bloodtinged, turbid fluid. Both lungs showed a patchy pneumonia.

The small bowel showed scattered areas of injection, and contained a long, yellow tapeworm, identified as *Taenia saginata*. The head of the worm was not attached to the mucosa of the bowel at the time of autopsy.

One of the mesenteric arteries showed panarteritis with thrombosis, but there was no evidence of infarction in the area of small bowel supplied by that artery.

A typical, focal, exudative nephritis was present, together with a small, anemic infarct in the right kidney.

The liver was the seat of passive congestion.

The brain showed scattered capillary thrombi and small perivascular hemorrhages.

Bacterial cultures taken from the valvular vegetations at autopsy yielded a pure growth of *Streptococcus fecalis*.

Anatomic Diagnosis.—Productive and fibrinous polypoid endocarditis, mitral and aortic valves; mitral stenosis; focal productive myocarditis; productive pericarditis, localized; patchy pneumonia, bilateral; massive septic infarct, spleen; fibrinous and purulent peritonitis; tapeworm, small intestine (*Taenia saginata*); focal exudative nephritis; septic infarct, right kidney; passive congestion, liver; panarteritis, mesenteric artery, with septic thrombosis.

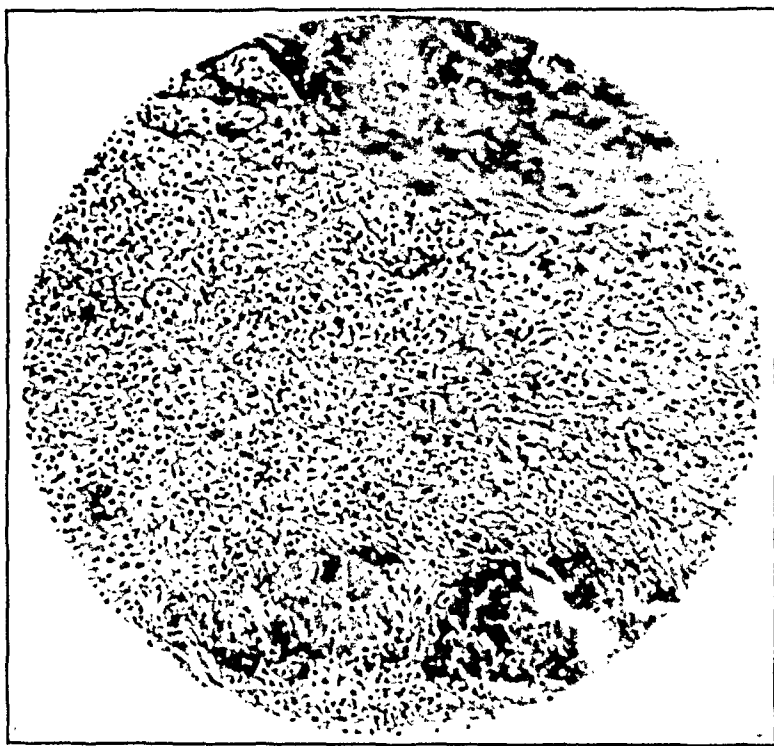


Fig. 2.—High-power view of mitral vegetation. Disintegrating leucocytes are held in a fibrin meshwork.

DISCUSSION

This case stands on the borderline between acute and subacute bacterial endocarditis. There was a history of previous rheumatic valvular disease, followed by an attack which had rather vague beginnings and ended in death, after running a course of approximately nine to ten weeks. The final illness was characterized, chiefly, by weakness, lassitude, dyspnea, anemia, vague pains, fever, loss of weight, clubbing of the fingers, and by outward evidences of embolic phenomena, enlargement of the spleen, and hematuria with albuminuria. Petechiae were not observed while the patient was in the hospital. However, she noticed a

tender, red elevation on her right thumb one week before admission. This may have been an Osler's node. The autopsy findings confirmed the clinical diagnosis.

Another feature worthy of note was the peritonitis, which was confined mostly to the left side and apparently related to a massive splenic infarction. Several instances of peritonitis following rupture of the spleen in cases of subacute bacterial endocarditis have been reported, but in this case the capsule of the organ was found intact at autopsy. It is reasonable to suppose that the infecting organisms passed from the necrotic infarcted area through the capsule to the abdominal cavity. Clinical examination revealed that abdominal tenderness and rigidity of the abdominal muscles were observed several days before death.

Of interest also, was the discovery of a long tapeworm in the small intestine. This may explain the diarrhea, which was of fairly long standing.

The isolation of *Streptococcus fecalis* from the blood stream in life, and from the mitral vegetations at autopsy, is the most noteworthy feature. It raises a question, discussed briefly above: How frequently is subacute bacterial endocarditis caused by *Str. fecalis* or other organisms of the enterococcus group? Judging from the literature, the occurrence is rare. There is some reason to believe that it may be more frequent than is generally suspected, as careful bacteriologic work is necessary for the proper identification of the organism.

SUMMARY

1. A case of *Streptococcus fecalis* endocarditis, with autopsy findings, in a 30-year-old woman with rheumatic valvular disease, is reported.

The organism was isolated from the blood stream during life, and from the heart valves at autopsy.

2. Peritonitis caused by splenic infarction without rupture of the spleen was observed.

REFERENCES

1. Sherman, J. M., Mauer, J. C., and Stark, Pauline: *Streptococcus Fecalis*, J. Bact. 33: 275, 1937.
2. Clements, A. B.: *Enterococcus Endocarditis*, New York State J. Med. 1937, 1842-1844.
3. Andrewes, F. W., and Horder, T. J.: A Study of the Streptococci Pathogenic for Man, Lancet 12: 708 and 779, 1906.
4. Sherman, J. M.: The Enterococci and Related Streptococci, J. Bact. 35: 81, 1938.
5. Sherman, J. M.: The Streptococci, Bact. Rev. 1, 1937.
6. Horder, T. J.: Endocarditis, Lancet 1: 695, 745, and 850, 1926.
7. Subacute Bacterial Endocarditis (Extensive Survey of the Literature), Annals of the Pickett-Thompson Research Laboratory IV, part 1, 173, 1928, London, Balliere, Tindall, and Cox.

THE CARDIAC MECHANISM IN A FATAL CASE OF ACUTE THYROTOXICOSIS

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THE role of the thyroid gland in the production of cardiac dysfunction, and even cardiac failure, is well recognized. That the cardiac derangement may be the only apparent clinical manifestation of hyperthyroidism was brought out by the investigations of Levine and Sturgis, in 1924.¹ Recently we have been afforded the opportunity of observing the terminal cardiac mechanism during a thyroid crisis which ended fatally. The electrocardiographic studies were made during the last few hours of life, and we believe that they record the mode of cardiac death in thyroid crisis more accurately than tracings² which have shown only the last few heart beats after the patient was, from the clinical point of view, dead.

CASE REPORT

B. W. S., Med. No. 54135, a 41-year-old, unemployed white man, entered the hospital for the first time Dec. 27, 1938, complaining of generalized weakness. He had been well until October, 1938, at which time he noted the onset of a nonproductive cough, mild fever, and generalized prostration, severe enough to confine him to bed intermittently. Fluoroscopic and roentgenographic examinations of the chest were reported as negative by his family physician. He became increasingly irritable, apprehensive, and fatigued. In December, 1938, he had a low-grade, intermittent fever, associated with a systolic murmur at the apex, but without other cardio-respiratory symptoms. He had been sleeping well, had had only a fair appetite, and had lost approximately twenty pounds in the preceding two years. The past history was unimportant. The family history was significant only in that his father had died of angina pectoris and his mother had active pulmonary tuberculosis. The marital and social history revealed much domestic conflict. He had been unemployed for two years, during which time he had been dependent upon friends and relatives.

Physical Examination.—The patient was a restless, well-developed, well-nourished, middle-aged man. He was agitated, but his speech was coherent and his mentality clear. His temperature was 99.2° F., his pulse rate 96, and his respiratory rate 25. The skin was warm and moist. The palms, axillae, and groins were bathed in sweat. Examination of the eyes, including the fundi, was negative. There was no exophthalmos or lid-lag. The thyroid gland was not enlarged to palpation, and presented no bruit. The lungs were negative. The heart was not enlarged; the apex impulse was forceful and diffuse. The retromanubrial dullness was not increased. The cardiac rhythm was normal. The first sound was snapping in character, with a moderately loud systolic murmur, most intense at the apex. There were no diastolic murmurs. The blood pressure was 170/100. The deep reflexes were hyperactive, but equal. The extended fingers showed a fine tremor. The remainder of the examination was negative.

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Received for publication June 19, 1939.

Laboratory Examination.—The urine, blood, and stool were normal. The blood Wassermann reaction was negative. The corrected sedimentation rate was within normal limits. *Streptococcus hemolyticus* skin tests showed the presence of sensitivity. Two blood cultures remained sterile. The basal metabolic rate (Dec. 29, 1938) was plus 32. Roentgenologic examination of the chest was negative, showing no evidence of substernal thyroid enlargement.

Clinical Course.—The patient's course in the hospital was uneventful. The pulse rate ranged between 90 and 100 during his four-day stay. He was thought to have mild hyperthyroidism and was advised to remain for further observation to confirm the diagnosis. However, on his wife's insistence, he left the hospital against advice, with permission to return.

(Second Admission, Med. No. 54430). The patient re-entered the hospital Feb. 11, 1939. During the interim, after feeling well for one week after discharge, he had suffered a recurrence of all his previous symptoms. Nervousness was now associated with sleeplessness and mild palpitation. He had maintained his weight, although his appetite remained only fair. Two days prior to entry he was in an automobile accident in which he suffered no obvious physical trauma. However, he claimed to have undergone a severe emotional shock, necessitating his confinement to bed. Subsequent information revealed that a damage suit had been instituted.

Physical Examination.—The patient was much more agitated and voluble than on his first admission. One observer felt that there was slight exophthalmos. The thyroid now showed slight diffuse enlargement but presented no bruit. The heart was essentially the same as at the first examination. The blood pressure was 122/68. The heart rate was 125, the rhythm normal. The tremor of the fingers was more noticeable. The remainder of the examination revealed nothing not present on the first admission.

Laboratory Examination.—The basal metabolic rate was plus 65 and plus 70, on Feb. 13 and Feb. 14, respectively. Other studies showed nothing abnormal.

Clinical Course.—The patient's condition remained essentially unchanged until the evening of Feb. 14, at which time he became very agitated, jumping in and out of bed, attempting to leave the hospital, weeping loudly, and apparently suffering from an acute hallucinosis. He became unmanageable, and required sedatives and restraints. On Feb. 15, the administration of Lugol's solution, in doses of 10 minims three times daily, was begun. He continued to be hyperactive despite the administration of sedatives, and fluids parenterally. Some observers felt that he was suffering from a toxic delirium, possibly secondary to his repeated medications rather than to his hyperthyroidism. Accordingly, all medications except iodine were withdrawn for a twelve-hour period, and fluids were forced parenterally. He continued to grow worse on this regimen. It became necessary to use paraldehyde in frequently repeated doses. On Feb. 17 and 18, Lugol's solution was given intravenously in 3.0 c.c. doses, in addition to that given orally. When not under the influence of sedatives, the psychotic manifestations reappeared. During this period of time the temperature ranged between 98.2° and 100.4° F., the pulse rate between 90 and 125, the respiratory rate between 30 and 45, and the blood pressure remained near the admission level.

On Feb. 18, at 10:40 P.M., the radial pulse suddenly became thready, and the patient appeared dusky and cyanotic. The respirations were rapid and shallow, remaining so in spite of the administration of oxygen intranasally. Auscultation of the heart revealed a regular apical rate of 180, uninfluenced by vagal stimulation. At 10:50 P.M., the heartbeat had become absolutely irregular, with a ventricular rate between 250 and 325 (Fig. 1a). At 11:00 P.M., the cardiac mechanism abruptly changed spontaneously to a slow normal sinus rhythm, with a rate of 79.6 (Fig. 1b). Thereafter the rate increased gradually until a dominant rate of 195 became established (Fig. 1c and d). The blood pressure at this time was 110/70. At

11:30 P.M., 10 c.c. (0.5 gm.) of "digalen" were administered intravenously. Auscultation and serial electrocardiograms revealed no changes in the cardiac mechanism. A second 10 c.c. (0.5 gm.) dose of "digalen" was injected intramuscularly at 12:45 A.M. An electrocardiogram fifteen minutes later revealed persistence of the normal sinus tachycardia, with a rate of 145.2 (Fig. 1c). At 1:04 A.M., he suddenly became very cyanotic, the heart sounds became very weak and distant, and the blood pressure unobtainable. At this time the apical rate was 100. Within two minutes, coarse bubbling râles appeared throughout both lungs, the heart tones were not heard, and respirations ceased. Artificial respiration and stimulants were of no avail. Electrocardiograms taken during this final interval (Fig. 1 f and g) revealed marked sinus bradycardia and ventricular standstill.

Summary of Post-mortem Examination.—The heart weighed 350 gm. There was no evidence of enlargement, hypertrophy, or dilatation. The valves were thin, membranous, freely movable and showed no vegetations. The posterior cusps of the aortic valves were fused for a distance of 0.8 centimeter; the valve margins were not rolled. The myocardium was a deep reddish brown, with no evidence of fibrosis or infarction. The coronary arteries were patent. *Lungs:* The right lung weighed 550 gm., the left, 620 gm. The cut surfaces of the lungs showed uniform, marked, passive congestion, without evidence of pneumonia. The liver weighed 1540 gm. Its consistency was soft, and it had a light reddish-brown color and a faintly granular surface. The capsule was thin, shiny, and glistening. The cut surface showed a sharp edge, with well-differentiated liver markings due to congestion and closely resembling the nutmeg mottling of cardiac cirrhosis. There was no evidence of bile stasis, foci of necrosis, or thrombosis. The thyroid gland weighed 57 gm. It was symmetrically enlarged, with evidence of hyperplasia and increase in colloid. There was a small cystic area at the right upper pole, but no evidence of fibrosis or inflammation.

Microscopic Examination.—The myocardium showed no inflammatory reaction or increase in connective tissue stroma. There was considerable edema of the interstitial tissues. No Aschoff bodies were seen. No areas of true degeneration of muscle fibers were found. *Lungs:* The veins were moderately engorged. The alveolar walls were slightly swollen. *Liver:* There was an apparent increase in connective tissue in many of the central areas. There were recent infarcts of varying size, about central or mid-zone in location; the cord cells in these areas were pale red, the erythrocytes having faded. No thrombi were seen. There was no increase in periportal connective tissue. *Thyroid:* The acini varied in size and shape; most of them contained large masses of desquamated epithelial cells, mixed with colloid varying from pale pink to deep blue. Better preserved acini showed infolding of epithelium, and its tall columnar type was evident. The stroma was not increased.

Anatomic Diagnosis.—Hyperplasia of thyroid, with slight iodine involution; edema of lungs; focal infarcts of liver; passive congestion of lungs, liver, spleen, and kidneys; cirrhosis of liver (cardiac); hyperplasia of thymus; hyperplasia of aberrant thymus; congenitally bicuspid aortic valve.

DISCUSSION

The frequency of paroxysmal auricular fibrillation in hyperthyroidism has been commented upon by many investigators, among them Barker, et al.,³ Nicholson,⁴ Ernstene and Mulvey,⁵ and Hay.⁶ In our case the cardiac mechanism remained normal, although the rate was rapid, until the terminal episode, during which paroxysmal auricular fibrillation with an extremely rapid ventricular rate appeared. It was observed that,

just prior to the first electrocardiogram here reproduced, the heart rate changed abruptly from 125 to 180. The beating was regular, there was no pulse deficit, and vagal stimulation was without effect. Within ten minutes the beating became completely irregular. The electrocardiogram taken at that time (Fig. 1*a*) shows auricular fibrillation with a ventricular rate ranging between 250 and 300; in places, small groups of beats reached a rate of 325. At one point in Lead I (marked X), there are two consecutive beats which we interpret as ventricular extrasystoles. They resemble beats which inaugurate ventricular tachycardia. Following the maintenance of fibrillation at this rapid rate for ten minutes, there was an abrupt, spontaneous change to a slow, normal, sinus rhythm (Fig. 1*b*), which became progressively more rapid until it

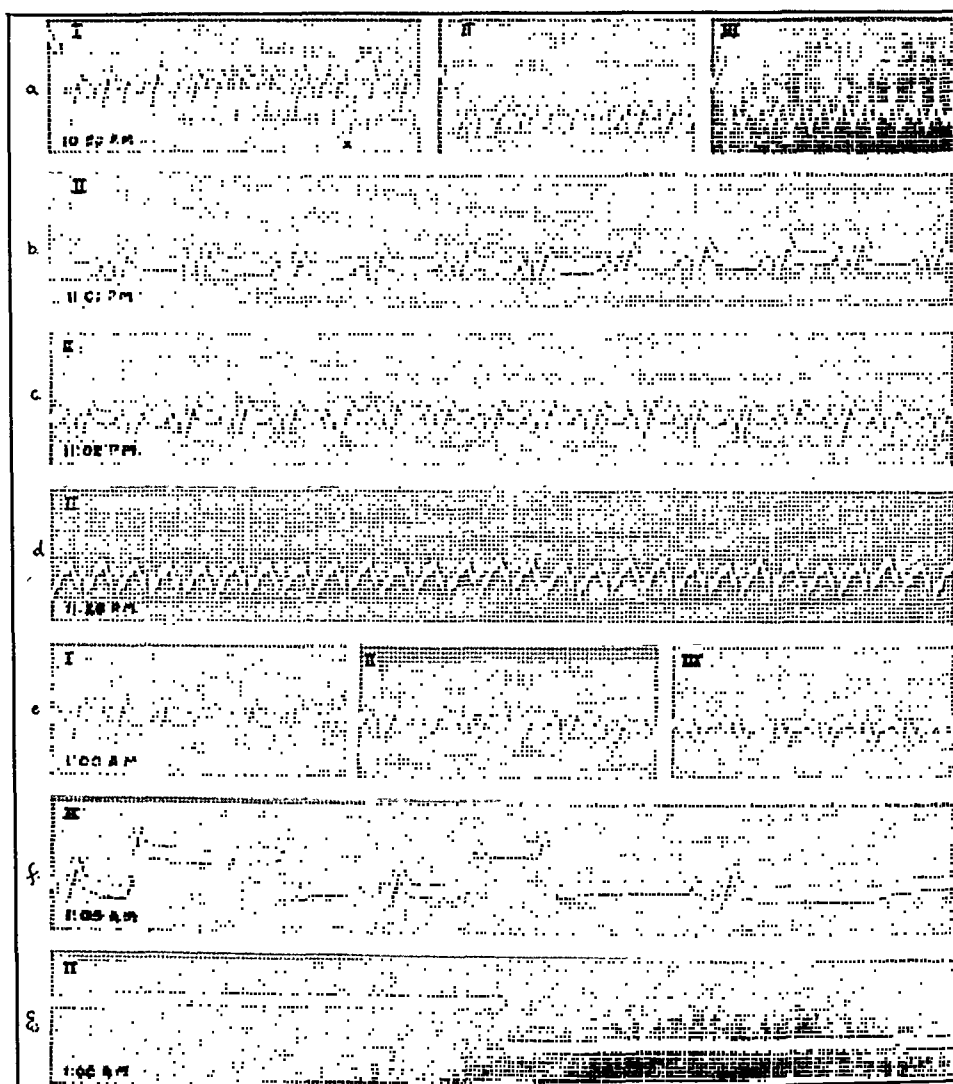


Fig. 1.—Electrocardiographic records during final hours of life in a case of acute thyrotoxicosis. *a*, 10:50 P.M., auricular fibrillation, ventricular rate 250 to 325. Ventricular extrasystoles marked X in Lead I. *b*, 11:01 P.M., normal sinus rhythm, ventricular rate 79.5, with peculiar, short duration of R-T complex. *c*, 11:02 P.M., sinus tachycardia, ventricular rate 125.8. *d*, 11:25 P.M., sinus tachycardia, ventricular rate 196.6. *e*, 1:00 A.M., patient had received 20 c.c. (1.0 gm.) of "digalen," sinus tachycardia, ventricular rate 145.2. *f*, 1:05 A.M., the dying heart. *g*, 1:06 A.M., two minutes after death had occurred, as ascertained clinically.

reached a rate of 195.6 (Fig. 1*c* and *d*). This sinus tachycardia was only slightly affected by digitalis (Fig. 1*e*), which is the type of response to the drug observed by Barker, et al.,³ Nicholson,⁴ and Grant⁷ in cases of hyperthyroidism. After the rate had been maintained for ninety-five minutes, the heart gradually slowed, and the terminal cardiac mechanism can be seen to be one of bradycardia and ventricular standstill (Fig. 1*f* and *g*). It is of interest to note that in all of the records in which there is a normal response to the auricular impulse, the duration of the R-T complex is quite short, even when the heart rate is very slow.

A review of the literature discloses only a few reports concerning the exact character of the terminal cardiac mechanism in hyperthyroidism. Goodall⁸ was of the opinion that ventricular fibrillation was the actual cause of sudden death during acute thyrotoxicosis following operation upon the thyroid gland. Cookson⁹ concluded that sudden death in cases of auricular fibrillation associated with various types of heart disease was due to fibrillation of the ventricles. Willius, et al.,¹⁰ McEachern and Rake,¹¹ and Hamilton¹² have reported series of patients observed clinically, and have described the mode of death in thyroid crisis. Their reports agree, in that the majority of the patients showed no clinical evidence of congestive failure, a fact borne out in the case here presented. Their case reports are uniform, in that all of the patients had rapid heart rates, though there was no consistency about the nature of the cardiac mechanism. However, in none of these published reports are we able to find electrocardiographic observations of the actual, final, cardiac mechanism. Levine¹³ has pointed out that, viewing the arrhythmias of hyperthyroidism as a whole, the great majority are auricular in origin. The terminal cardiac mechanism in this case can be seen to be a rapid auricular arrhythmia, followed by bradycardia and ventricular standstill. It is suggested that death was due to exhaustion of the myocardium.

The authors wish to acknowledge their appreciation of the valuable suggestions and assistance of Dr. Samuel A. Levine in this study, and of the aid of Dr. G. Darrell Ayer in the review of the pathologic material.

REFERENCES

1. Levine, S. A., and Sturgis, C. C.: Hyperthyroidism Masked as Heart Disease, Boston M. & S. J. 190: 233, 1924.
2. Sigler, L. H., Stein, I., and Nash, P. I.: Electrocardiographic Changes Occurring at Death, Am. J. M. Sc. 194: 356, 1937.
3. Barker, P. S., Bohning, A. L., and Wilson, F. N.: Auricular Fibrillation in Graves' Disease, AM. HEART J. 8: 121, 1932.
4. Nicholson, B. C.: The Cardiac Arrhythmias of Thyrotoxicosis with Special Reference to Prognosis, St. Barth. Hosp. Rep. 70: 129, 1937.
5. Ernstene, A. C., and Mulvey, B. E.: A Study of Auricular Fibrillation Following Operations for Goiter, Am. J. M. Sc. 188: 382, 1934.
6. Hay, J.: The Thyrotoxic Heart, with Special Reference to "Masked Hyperthyroidism," Lancet 2: 1377, 1936.

7. Grant, S. B.: The Management of Goitre Patients with Congestive Heart Failure, *M. Clin. North America* 11: 569, 1927.
8. Goodall, J. S.: The Heart in Graves' Disease, *Practitioner* 105: 37, 1920.
9. Cookson, H.: The Aetiology and Prognosis of Auricular Fibrillation, *Quart. J. Med.* 23: 309, 1930.
10. Willius, F. A., Boothby, W. M., and Wilson, L. B.: The Heart in Exophthalmic Goiter and Adenoma with Hyperthyroidism, *M. Clin. North America* 7: 189, 1923.
11. McEachern, D., and Rake, G.: A Study of the Morbid Anatomy of Hearts from Patients Dying with Hyperthyroidism, *Bull. Johns Hopkins Hosp.* 48: 273, 1931.
12. Hamilton, B. E.: Heart Failure of the Congestive Type Caused by Hyperthyroidism, *J. A. M. A.* 83: 405, 1924.
13. Levine, S. A.: Personal Communication.

Department of Reviews and Abstracts

Selected Abstracts

Plotz, Milton: Asthmatoïd Heart Failure; a Form of Left Ventricular Failure and Its Differentiation From Bronchial Asthma by Circulation Time and Other Criteria. *Ann. Int. Med.* 13: 151, 1939.

Wheezing respiration is common in left ventricular failure. It may occur without basal râles ("asthmatoïd heart failure") in which case it closely simulates allergic asthma in symptoms, physical signs, and response to adrenalin.

The pathogenesis is discussed and illustrative cases are given.

The quickest and easiest method of determining whether or not a case of paroxysmal dyspnea is cardiac in origin is by means of a study of the circulation times which show decreased blood velocity in the pulmonary circuit. Arm-to-carotid (cyanide) and arm-to-lung (ether) times may be quickly and accurately determined at the bedside. They are more reliable in the differential diagnosis than determinations of the venous pressure.

AUTHOR.

Dry, Thomas J., and Willius, Fredrick A.: Interpretation of the Electrocardiographic Findings in Calcareous Stenosis of the Aortic Valve. *Ann. Int. Med.* 13: 143, 1939.

The electrocardiographic findings in 176 cases of calcareous stenosis of the aortic valve are presented. The records were analyzed with special reference to graphic configurations conforming to the generally accepted laws of predominant ventricular strain. A very high correlation between electrocardiographic variations and pathologic lesions was disclosed for the post-mortem material, only eight cases proving to be exceptions to the rule.

In clinical cases the same opportunity for comparable correlations was obviously not afforded, although a similar tendency toward correlation was disclosed when the data on the post-mortem cases were applied to them.

Auricular fibrillation occurred infrequently, only twenty-five instances (14.2 per cent) being recorded for the entire series. In six cases auricular fibrillation occurred in the presence of mitral stenosis and aortic insufficiency, and in seven other cases in the presence of aortic insufficiency alone.

AUTHORS.

Helwig, Ferdinand C., and Wilhelmy, Ellis W.: Sudden and Unexpected Death From Acute Interstitial Myocarditis: A Report of Three Cases. *Ann. Int. Med.* 13: 107, 1939.

Three cases of acute interstitial myocarditis causing sudden and unexpected death are reported. In all instances a laborious microscopic examination of the myocardium was necessary before the lesion was found. The necessity for painstaking histologic investigation of the myocardium in sudden death is obvious.

Acute interstitial myocarditis may be the sole cause of sudden and unexpected death.

AUTHORS.

Lowell, T. C.: The Significance of Myocardial Scars in the Human Heart. *J. Path. & Bact.* 49: 195, 1939.

In a series of five cases, myocardial scars in the ventricle were reconstructed and are described in detail. These scars were shown to have an anatomic position consistent with their being a portion of one of the various muscle groupings of the ventricles. It is suggested that they represent the end stage of a type of myocardial infarction due to interference with the blood supply to a portion of a muscle bundle though not necessarily the result of coronary thrombosis of embolism.

AUTHOR.

de Navasquez, S.: The Incidence and Pathogenesis of Myocardial Lesions in Subacute Bacterial Endocarditis. *J. Path. & Bact.* 49: 33, 1939.

Myocardial lesions whose characteristics have been defined, were encountered in nineteen out of twenty cases of subacute bacterial endocarditis.

These lesions develop as a result of embolism of the coronary arteries of arterioles by fragments of vegetation which vary in size and bacterial content. They are specific only insofar as they show evidence of embolism and polymorphonuclear reaction.

No relationship was demonstrated to the degree of cardiac failure, the heart valve affected, the character of the vegetation, or the duration of the disease.

AUTHOR.

Fernando, P. B.: Rheumatic Heart Disease as Met With in Hospital Practice in Ceylon. *Quart. J. Med.* 8: 261, 1939.

The autopsy records of the General Hospital in Colombo, for the period of July, 1934, to November, 1937, have been studied for evidence of rheumatic carditis. The records of 215 patients admitted for rheumatic infections into the wards under the care of the author during this same period have been studied from the clinical point of view.

The post-mortem incidence of rheumatic carditis appears to be the same in Colombo General Hospital as in Guys and St. Mary's Hospitals in London. The incidence, manifestations, virulence, and progressiveness of the disease seem to be very little different from what they are in temperate climates.

The incidence of rheumatic infections was 2.2 per cent of the total admissions. The incidence of rheumatic carditis was 1.4 per cent of the total admissions and 21.5 per cent of cardiovascular admissions. Approximately one-third of the rheumatic cases had no evidence of carditis, while two-thirds had evidence of carditis. The above figures agree closely with similar figures for the five general hospitals in Victoria, Australia.

The clinical manifestations of rheumatic arthritis were in no way different from those of the conditions diagnosed as such in temperate climates.

The tendency to the occurrence of carditis was similar. Adolescents and young adults were those most liable; the manifestations of the carditis were also similar. Valvular lesions predominated as in other countries.

The commonest valvular lesion was mitral stenosis, and next in order of frequency came aortic regurgitation. Mitral lesions were eight times as numerous as aortic lesions.

Clinically evident pericarditis occurred in 6.9 per cent of the cases of rheumatic carditis.

Auricular fibrillation occurred in nearly a quarter of the patients above the age of 30 years who showed evidence of carditis. About two-thirds of the cases of auricular fibrillation were in patients with mitral stenosis. Auricular fibrillation and flutter therefore occurred in 16 per cent of all the cases of rheumatic carditis.

Uncomplicated rheumatic arthritis was commoner in males than in females, but carditis both in the acute and chronic forms occurred more frequently in the female.

Over four-fifths, both of the cases and of the deaths, were in patients below 41 years of age. The heaviest incidence was in the two age groups between 21 and 40 years. The above figures show that in Ceylon also rheumatic carditis is a disease of adolescence and early adult life, and the majority of patients so affected die before they reach the age of 40 years.

There was no greater susceptibility to rheumatic infection in any one of the races inhabiting the island.

All the cases studied were in the poorer classes of the population, and factors common to all were overcrowding and malnutrition.

The incidence of chorea in this series was only one-third of that in Victoria, Australia.

Subcutaneous rheumatic nodules were not met with; they are supposed to be rare in Ceylon.

AUTHOR.

Wood, J. Edwin, Jr., and Cash, James R.: Obesity and Hypertension: Clinical and Experimental Observations. Ann. Int. Med. 13: 81, 1939.

The literature indicates a definite association between obesity and systolic blood pressure elevation in a fair number of instances.

Systolic blood pressure in normal and hypertensive dogs rises with weight gain and falls with weight loss, while diastolic pressure varies little.

These observations do not indicate that obesity is a cause of essential hypertension but support the idea that overweight may be a factor of importance in the elevation of systolic blood pressure.

AUTHORS.

Williams, Denis, and Lennox, William G.: The Cerebral Blood-Flow in Arterial Hypertension, Arteriosclerosis, and High Intracranial Pressure. Quart. J. Med. 8: 185, 1939.

Simultaneous samples of blood were obtained from an artery and from an internal jugular vein in forty patients with high intracranial pressure, arterial hypertension, or cerebral arteriosclerosis, and from a control group of forty-one persons without any of these disorders. The blood-gas contents were determined, and the arteriovenous differences and coefficients of oxygen utilization were used to estimate the relative cerebral blood flow of the groups.

The total cerebral blood flow of the groups with arterial hypertension and high intracranial pressure was normal.

The group with cerebral arteriosclerosis had a mean cerebral blood flow of 15 per cent below that of the control group. All the individuals in this group fell within normal limits, but none had a faster flow than the normal mean, due to mechanical limitation of the vascular bed.

It is therefore concluded that the cerebral blood flow is not significantly altered by high intracranial pressure, arterial hypertension, or by cerebral arteriosclerosis without hypertension.

The mechanism whereby the cerebral blood flow is maintained at a constant level in spite of extreme factors tending to the contrary is discussed.

AUTHORS.

Edwards, Edward A.: Chronic Organic Arterial Disease. *New England J. Med.* 221: 251, 1939.

This is a review of the pathology, diagnosis, and treatment of peripheral arterial occlusion caused by arteriosclerosis and thromboangiitis obliterans. The author points out that a patient can never expect a return of perfect function in the affected limb since the collateral vessels, although they may equal in the aggregate the caliber of the blocked artery, cannot transmit the quantity of blood passing through the previously normal arteries. In the small collateral arteries the pulse wave is damped and the blood oozes through under a lowered pressure. This, however, does not diminish the importance of therapeutic attempts to increase blood flow through collateral vessels.

NAIDE.

Symposium on Heart Disease, American Roentgen Ray Society, Sept. 20, 1938.

1. **Hodges, Fred Jenner: Determination of Heart Size.** *Am. J. Roentgenol.* 42: 1, 1939.

Procedures designed to estimate cardiac size by roentgen methods are available but it does not follow that measurements of this sort can be made with great exactitude, nor is it true that exact heart size determination is essential to good diagnosis. It is one matter to attempt heart size measurements in selected normal individuals, quite another to attempt such procedures in the case of many individuals where knowledge regarding exact heart size may be of paramount importance to the clinician in determining the diagnosis or observing the effects of treatment. A great variety of situations commonly encountered by roentgenologists, contrive in one way or another to defeat attempts to provide accurate cardiac measurements.

The continued search by means of experimental and clinical observation for a truly accurate method of heart size determination during life will, and should go on. For, if this goal can be achieved, new fields of usefulness can be explored. The ambition of cardiologists to develop some reliable method of estimating cardiac reserve and thereby to evaluate with accuracy the disability produced by various cardiac lesions is a worthy one.

AUTHOR.

2. **Robb, George P., and Steinberg, Israel: Visualization of the Chambers of the Heart, the Pulmonary Circulation, and the Great Blood Vessels in Heart Disease.** *Am. J. Roentgenol.* 42: 14, 1939.

The results obtained by visualization of the chambers of the heart and the thoracic blood vessels in patients having rheumatic, syphilitic, hypertensive, and arteriosclerotic cardiovascular disease are reported and their value is discussed. Visualization in heart disease as in the normal gives a detailed picture of the cardiovascular system in which each major structure can be examined separately and its characteristics observed. As a result it has been possible to determine accurately the location and the degree of the gross pathologic changes, thereby providing a means of solving certain hitherto perplexing problems.

The prominence of the pulmonary arc in the frontal view in our patients with rheumatic mitral stenosis and insufficiency was caused directly by the dilated pulmonary artery and not by the enlarged pulmonary conus or the left atrium; the left auricle formed the convexity immediately below the pulmonary arch. Elevation of the left bronchus was not caused by the left atrium but apparently by engorged pulmonary veins. In syphilitic aortitis, the intracardiac portion of the aorta, the most frequent site of involvement and one previously invisible, was outlined and the exact size, shape, and location of aneurysms of the aorta was determined. The degree of left ventricular hypertrophy and dilatation, the tortuosity and unfolding of the thoracic aorta, the "buckling" of the innominate artery and the identity of the vessel forming the anterior boundary of the "aortic triangle" were demonstrated in hypertensive heart disease. In the patient with arteriosclerotic cardiovascular disease, the heart was found to be normal in size, the apparent enlargement in the conventional roentgenogram being due to the deviated spine, whereas the aorta exhibited a moderate degree of dilatation, elongation, and unfolding with calcification and thickening of the wall.

From these preliminary observations it seems apparent that inference regarding the condition of the heart which is based upon grossly indirect evidence such as the alteration of the cardiac silhouette and the disturbance of adjacent structures can now be largely replaced by exact information obtained by separate visualization of the four chambers of the heart and the great blood vessels. As a consequence, the interpretation of conventional roentgenoscopy and roentgenography will become more accurate, enhancing the value of these widely used clinical methods of examination and ultimately making visualization of the chambers of the heart and the thoracic blood vessels necessary only in cases presenting unusually difficult diagnostic problems.

AUTHORS.

3. Freedman, Eugene: Inflammatory Disease of the Pericardium. *Am. J. Roentgenol.* 42: 38, 1939.

Pericardial effusion leads to the formation of cardiac configurations which have been described by various authors as bag- or pear-shaped, or resembling a round bottle with a short neck. None of these configurations, however, are typical of pericardial effusion. They may be produced by decompensated hearts also. The best differential diagnostic sign between a decompensated heart and pericardial effusion is the one described by Holmes. This is based on the change of cardiac configuration during changes in the position of the patient. Unfortunately this procedure cannot be utilized in patients who are orthopneic. The kymographic examination may be helpful in differentiating pericardial effusions from decompensated hearts. Berner observed vigorous pulsations of the aortic knob and decreased pulsations of the left ventricular region on the kymogram of a patient suffering from pericardial effusion. After the effusion disappeared the kymographic recording of the pulsatory amplitude of the left ventricle and aortic knob became equal.

The recognition of early pericardial effusion may be facilitated by finding an abnormally convex bulging of the posterior surface of the heart either roentgenoscopically or on the lateral roentgenogram (Fleischner). The most reliable method is the daily roentgen examination of the heart and the finding of considerable change in its size within short periods of time. Kienböck's inflammatory diverticulum of the heart represents an encapsulated pericardial effusion, most commonly on the right border. The remaining part of the pericardial cavity is usually obliterated.

Cardiac compression due to pericardial scar formation is usually represented on roentgen examinations by a normal-sized or smaller than normal heart. Moderate or marked enlargement of the cardiopericardial shadow is uncommon and may be due either to an unusually marked thickening of the pericardium or to an underlying valvular or myocardial disease.

The majority of the compressed hearts are either triangular or, less commonly, globular. In rare instances a compressed heart may show a mitral or aortic configuration. The cardiac pulsations are usually diminished or absent. Occasionally, however, certain sections of the compressed heart may show vigorous pulsations. The aortic knob is flattened or completely obliterated in the majority of compressed hearts. Due to the marked thickening of the pericardium, the heart becomes rigid and in the majority of cases its configuration remains either unchanged or changes but little during the two phases of respiration. The adhesions between the heart and pericardium lead to a fixation of the heart. The degree of fixation is determined with the aid of expiratory and inspiratory posteroanterior roentgenograms taken with the patient lying on either side and with lateral views taken during both inspiration and expiration. The most conclusive sign of cardiac compression, the calcification of pericardium, is present only in the minority of instances (in nine among twenty-six patients). The kymographic examination is of no differential diagnostic value in cardiac compression. It only serves as a record which enables one to compare the difference between the pulsatory amplitude before and after removal of the pericardial scar.

AUTHOR.

4. Sosman, Merrill C.: Roentgenological Aspects of Acquired Valvular Heart Disease. *Am. J. Roentgenol.* 42: 47, 1938.

Acquired valvular heart disease results in cardiac enlargement in almost every case and causes typical changes in the cardiac contour in the great majority.

Enlargement of the left auricle is one of the most reliable signs of mitral valvular disease.

The contour of the heart in aortic valvular disease may be duplicated by hypertensive heart disease but the differentiation can frequently be made by roentgenoscopy—in aortic regurgitation by the “rocking beat” and in aortic stenosis by demonstrating calcification in the aortic valve.

Calcification in aortic and mitral valves is frequently demonstrable roentgenoscopically and adds considerably to the accuracy in both structural and etiological diagnosis.

AUTHOR.

5. Levene, George: Roentgenologic Aspects of Non-Valvular Disease of the Heart. *Am. J. Roentgenol.* 42: 60, 1939.

Nonvalvular disease of the heart and various forms of myocardial insufficiency frequently produce distinctive roentgenologic appearances. Careful roentgenologic study is therefore well suited to the identification and appraisal of disturbed cardiac dynamics. Its importance is further increased by its ability to depict the relationship of the greater and lesser circulation in the individual case. It offers confirmatory evidence of a diagnosis established by other clinical methods and frequently assists in the differentiation of the causes of cardiac enlargement and decompensation.

AUTHOR.

6. Roesler, Hugo: Roentgenology of Congenital Cardiovascular Disease. Am. J. Roentgenol. 42: 72, 1939.

The author describes four groups of roentgenologic aspects of structural anomalies.

First, cases without any roentgenologic indication of the presence of defects; for example, the isolated interventricular septal defect of small size.

Second, deviations from the normal which are not characteristic for a congenital anomaly; for example, a general cardiac enlargement in the presence of a two- or three-chambered heart.

Third, certain conditions which reveal fairly characteristic features such as *coeur en sabot* or the large globular heart with marked enlargement of the pulmonary conus.

Fourth, structural anomalies with unequivocal roentgenologic findings.

McCULLOCH.

7. Sussman, Marcy L.: Roentgen Examination of the Aorta and Pulmonary Artery. Am. J. Roentgenol. 42: 75, 1939.

Well-defined deviations from the normal in the size of the aorta yield evidence of disease. Methods of measurement do not permit of precise determination of minor deviations, particularly in the ascending portion. Experience in roentgenoscopy of the chest, particularly as it permits observation of the variations in the great vessels due to the position of the diaphragm, of posture, of chest deformity and of age, has appeared more valuable than rigid application of mensuration. The smaller the deviation from normal the less valuable and sometimes more confusing is the information obtained. The roentgen examination of the aorta may not prove particularly valuable in the early diagnosis of luetic aortitis. Pulmonary artery dilatation, when not due to a congenital anomaly, is not characteristic of any particular disease but is rather an expression of the state of the pulmonary circulation.

As regards the two great vessels, if the roentgen findings are considered alone and completely apart from the clinical data, the value of the examination has been overestimated in the literature. In actual practice it has its definite place when considered as an integral part of the physical examination.

AUTHOR.

- Kerley, Peter: Intrathoracic Aneurysms. Brit. J. Radiol. 12: 158, 1939.

This study is based on a series of sixty-two cases of intrathoracic aneurysms observed in Westminster and Royal Chest Hospitals, over a period of ten years, in whom the diagnosis was affirmed either by autopsy or by combined clinical, radiologic and pathologic investigations.

With good technique and careful consideration of the clinical and radiologic evidence, correct diagnosis can be achieved in 90 per cent of the cases. If kymography is available, the correct diagnosis can be made in 98 per cent of the cases. Mistakes occur in dissecting aneurysms where there is no obvious tumor, and in cases where the tumor is concealed by a collapsed lung.

AUTHOR.

- Robb, George P., and Steinberg, Israel: Visualization of the Chambers of the Heart and the Thoracic Blood Vessels in Pulmonary Heart Disease: A Case Study. Ann. Int. Med. 13: 12, 1939.

Detailed visualization of the cardiovascular system demonstrated for the first time during life the nature and the extent of the pathologic changes in pulmonary heart disease.

Cardiovascular mensuration may now become an exact procedure since it can measure fundamental anatomic structures rather than arbitrary diameters having no anatomical counterpart.

The recognition of the early stages of pulmonary heart disease which hitherto could not be diagnosed should now be possible.

AUTHORS.

Gross, Robert E., Emerson, Paul, and Green, Hyman: **Surgical Exploration and Closure of a Patent Ductus Arteriosus.** *Surgery* 6: 201, 1939.

A case is reported of an 11-year-old boy who had typical physical and x-ray findings of a patent ductus arteriosus. As the child had been followed over a period of several years, there had been slight but definite hypertrophy (or dilatation) of the heart, this change being presumably caused by the large shunt between the aorta and pulmonary artery. From statistical evidence, the boy presumably was facing a rather high probability of subsequent cardiac failure of some degree because of the burden imposed by the ductus shunt. Furthermore, this congenital lesion carried with it a high risk of subacute bacterial endocardial infection. In the attempt to reduce the work of the heart imposed by the shunt and also to lessen the danger of subacute bacterial endarteritis, surgical exploration was undertaken for obliterating the ductus. The vessel was found to be 11 to 12 mm. in diameter and was successfully ligated. The patient stood the operative procedure with extremely little reaction.

AUTHORS.

Laplace, Louis B.: **Cardiovascular Complications of Fracture.** *Am. J. Surg.* 44: 161, 1939.

Five hundred hospitalized cases of fracture were analyzed with respect to cardiovascular complications. The mortality for the cases having a normal cardiovascular system was 1 per cent; for those having associated cardiovascular disease, 34 per cent. The vast majority of fracture patients who died had clinical evidence of arteriosclerotic cardiovascular disease and had sustained a broken hip. Death resulted in these cases from a form of slowly progressive peripheral circulatory failure. The various ways in which fractures may cause damage or functional impairment of the cardiovascular system are discussed.

AUTHOR.

Allen, Frederick M.: **Surgical Considerations of Temperature in Ligated Limbs.** *Am. J. Surg.* 45: 459, 1939.

The survival limit of the leg tissues of several mammalian species, deprived of circulation, is increased by reduction of temperature of the environment surrounding the ischemic limbs. At room temperature the survival limit of the leg tissues is above fifteen hours. Above room temperature gangrene and systemic shock occur in less than fifteen hours. Near 0° C. recovery is possible after ligation for fifty-four hours.

The applications of refrigeration to surgery of ischemic legs is discussed. Of special interest is the suggestion that the period during which embolectomy may be performed successfully is much longer at ice temperature than at higher temperatures.

NAIDE.

Hill, R. M.: Vascular Anomalies of the Upper Limbs Associated With Cervical Ribs. *Brit. J. Surg.* 27: 100, 1939.

A case is described of bilateral cervical ribs accompanied by vasomotor disturbances of the hands of the acrocyanosis type in which removal of a rib and fibromuscular band produced relief of pain, diminution of swelling, and improvement in the color changes of the hand on the corresponding side.

The symptoms of vasoconstriction were proved, at operation, to be caused by irritation of the lower trunk of the brachial plexus by the inner border of the cervical rib, a fibromuscular band and the scalenus anticus muscle.

NAIDE.

Blumgart, Herrman L., and Altschule, Mark D.: Should Digitalis Be Administered to Patients With Pre-existing Partial Heart Block? *Am. J. M. Sc.* 198: 455, 1939.

In treating patients with pre-existing partial heart block, the physician is not infrequently confronted with the difficult decision as to whether digitalis should be prescribed, because of the danger of further interference with the passage of impulses on the one hand, and clear indications for its administration on the other. So far as we are aware, no suitable body of evidence bearing on this question is available.

Nineteen patients ranging in age from 15 to 72 years were studied. Congestive heart failure was present in almost all subjects. In 3, a varying 2-to-1 and 1-to-1 relationship between auricular and ventricular contractions existed. In most of the patients prolongation of the P-R interval was due to coronary sclerosis; in the others, rheumatic heart disease was present.

A standardized preparation of digitalis was administered in doses calculated on the basis of body weight; in accord with general practice, somewhat less than the full Eggleston dosage was administered.

The results demonstrate that digitalis in doses sufficient to induce therapeutic effects may be given to patients with partial heart block without causing interference with the orderly passage of impulses from the auricles to the ventricles. The dosages employed were those usually employed in treating patients with congestive failure in the hospital; the adequacy of the amounts used was indicated by the therapeutic response; it was not considered germane to this study to give amounts which would produce toxic manifestations, although in 6 cases nausea occurred without change in the P-R interval.

The results of this study show that while digitalis and organic heart disease each result in interference with auriculoventricular conduction, these factors do not reinforce each other, and their simultaneous presence does not lead to an additive effect when doses in therapeutic amounts such as were used in the present study are utilized. The presence of partial heart block does not constitute a contraindication to the use of digitalis.

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**Executive Committee.*

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